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ORIGINAL ARTICLES

TREACHEROUS TRANQUILIZERS*

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During the past two decades advances in the fields of science and technology have accelerated beyond man's imagination. The present century has spawned a rapidly expanding family of "Ages," to wit: the Atomic and Hydrogen Age, the Age of Automation and, most recently, the dawn of the Space Age. Superimposed on these amazing technological advances there has developed, perhaps subconsciously, the Age of Anxiety. This, in itself, may represent one of the penalties of so-called "modern progress."

Whether we like it or not, we currently live and move and have our being (such as it is) in a "psychological century" and at midterm, more or less, find ourselves surrounded, fenced in and all but suffocated by a veritable galaxy of anxieties. We are anxious about the future of freedom, about the fate of our social mores and our democratic form of government. We are deeply concerned about the preservation of our beliefs, our American way of life, our educational system (or lack of it), and the problem of juvenile delinquency. Our changing economic system, our controversial military and foreign policies, the uncertain direction and lack of control of the Labor movement contribute to our discordant political philosophies and often conflict with our fundamental religious tenets. Since the solution or resolution of our multitudinous uncertainties is not apparent, we have developed a sense of national and international frustration manifested by Tension.

tension. According to Huxley[20] tension is a psychosomatic disorder characterized by cramping and painful self-centeredness resulting from man's egotistical blind-spot. The constant conflict between the fundamental drive of biological self-affirmation and the

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individual's ubiquitous urge to gregariousness leads to restlessness, uncertainty and worry. Frustration of man's dreams of self-transcendence by the cold, and often cruel, reality of his personal inadequacy leads to chronic inner discomfort; in short, to tension. To escape from himself he frequently indulges in transcendental thinking whereby he projects himself over and above things mundane and monotonous to the dream-world of make-believe, where unpleasant facts are replaced by delightful fantasies, bordering on the realm of schizophrenia.

On the other hand, if steered into productive channels and guided by acceptable moral standards, the drive to self-transcendence, and its accompanying tension, may be a positive and a creative force. The desire to improve himself, to earn a better living, to make bounteous provision for his family and to enjoy a higher station in life is generated by tension, which lights the fire of ambition. The flame of ambition is fed by self-denial.

However, if ambition be excessive and our "hero" unable to fulfill his dreams and yearnings, he then becomes frustrated. Unrequited frustration leads to chronic anxiety with loss of perspective, loss of efficiency and eventual loss of self-respect. To compensate for his failure to cope with the "enemy within," the frustrated individual seeks surcease from tension either by means of tranquilizing agents or by joining a crowd where he loses his personal identity and becomes engulfed in a tidal wave of self-transcendency.

Thus, the tense individual becomes an escape-artist when he joins a group or whenever he resorts to tranquilizers because he is more interested in self-satisfaction than he is in self-control. His immediate urge is to avoid his current tension with no thought for the morrow, completely oblivious of the fact that after the orgy must come the hangover. But, at best, the pursuit of happiness can be only a partial solution or a temporary palliative. This is true of all the tranquilizers, be they alcohol, opiates, the herd instinct or modern "drugs for the soul." Even the ancient Greeks had a word for it. They called their tranquilizers—usually wine, women and song—ataractics from the word "atarax," meaning "peace of mind."

TRANQUILIZING DRUGS. During the past 5 years a new series of pharmacologic agents has appeared which are said to produce peace of mind by relieving tension without the disadvantage of anesthesia and its sequential hangover. Such compounds were first employed in the overactive psychotic patient because they have a sedative, calming effect without enforcement of sleep.

In order to give an appropriate name to these new drugs, it was necessary to invent a new nomenclature. They usually are referred to as psychopharmacologic compounds since they influence the mind by effecting its morphologic substrate, the brain. But it is also true that tranquilizing agents act on the entire body with potent effects on the viscera, including the gastrointestinal tract, the cardiorespiratory system and the endocrine glands (Dews[6]).

Psychosomatic anxiety is the result of conflict between two equal and opposing ideas or feelings, each demanding overt expression. It is a symptom of a deep underlying disorder not curable by drugs. Thus, therapy with psychopharmacologic agents remains purely symptomatic in nature (Himwich[16]). Tranquilizers employed properly in a hospital or in a psychiatric institution under controlled conditions, to lead the patient back to or toward reality, are highly commendable. Their indiscriminate use in office practice,

or over-the-counter sales in a drugstore without prescription by a physician should be condemned rather than condoned (Bennett[3]).

At the present writing tranquilizing agents (Drill[8]) are divided into four main groups, based on their chemical classification, as follows: (a) rauwolfia alkaloids, (b) phenothiazine derivatives, (c) benzhydrol compounds and (d) agents which are derivatives of propanols.

(a) Reserpine is probably the best known of the rauwolfia alkaloids, which are primarily hypotensive agents and may be recognized, among other names, as Serpasil, Reserpoid, Sandril or Serpiloid. Rauwiloid is a form of alseroxylon[2]. Rauwolfia is marketed under the trade-name "Raudixin." Other alkaloids of the rauwolfia series include rescinnamine (Moderil) and deserpidine (Recanescine, Raumormine, and Harmonyl).

(b) The phenothiazine derivatives are represented by chlorpromazine (Thorazine), promazine (Sparine), prochlorperazine (Compazine), perphenazine (Trilafon), thiopropazate (Dartal) and mepazine (Pacatal).

(c) Benzhydrol compounds are listed as pipradrol (Meratran), azacyclonal (Frenquel), benactyzine (Suavital) and hydroxyzine (Atarax).

(d) Tranquilizing agents which are derivatives of the propanols include mephenesin (Tolserol) and meprobamate (Miltown; Equanil).

Newer compounds are appearing every hour almost on the hour but, by and large, they fall into one of the four major chemical categories listed above. More recently, the horizon has become tinted with a whole new group of chemopsychotherapeutic agents, which are isomers of ectylurea (Nostyn, and others). They produce mild sedation, are said to be non-habit-forming and may eventually replace the barbiturates.

There are approximately 100 brands of tranquilizers, each with a different trade name. The popularity of ataractics is phenomenal; last year physicians wrote 50 million prescriptions for "peace-pills." And all this, mind you, was for the "carriage-trade," for ambulatory patients who come to the office (Gerard[12]). The practitioner would do well to pause and remember that approximately 30% of patients react favorably to the administration of a placebo, which certainly is much less expensive and usually nontoxic!

The use of tranquilizing drugs in the veterinary profession is becoming all but notorious (Rice[27]). Tranquilizing agents are recommended for dogs to prevent the development of ulcers from too much worry, too much stress and strain, too much traffic, too much noise, too many boys and too many aggressive dogs in the neighborhood. Dowagers often personalize their pets by demanding tranquilizers for their cats or dogs before taking them to the Veterinarian's office.

CHOICE OF TRANQUILIZER. In the event it is decided to administer a drug to induce emotional calm in a human patient, choice of a tranquilizer should proceed according to the following criteria (Farah[10]):

1. It should produce a therapeutic response rapidly.
2. It should be effective in the majority of cases.
3. It should not produce addiction.
4. Its toxicity should be minimal in the therapeutic range.
5. Secondary side effects should be of low incidence.
6. Tolerance should not develop with continued use of the drug.
7. It should be suitable for both in- and outpatient therapy.
8. It should not dull the senses, decrease perception nor interfere with mental acuity.

Even if a perfect tranquilizer could

be found, it would fall far short of 100% effectivity because each patient is a problem unto himself and every medication must be personalized to that patient. Ideally, the physician should know the psychopharmacology of the medication and the psychodynamics of each patient. Unfortunately, the psychopharmacology of the tranquilizers is not completely known nor fully understood and the psychodynamics of personality varies from day to day with mood-swings.

The purpose of tranquilizing therapy is to reduce anxiety from a pathological state to one of normal degree and to control it within reasonable bounds so that the patient can learn to live with his anxiety. Thus, tranquilizers do not "cure" anything because they cannot attack the underlying basic personality-defect. Hence, too potent a tranquilizer, too high a dosage or too long an administration of low dosage will defeat the physician's purpose, and the last state of the patient will be worse than the first.

INDICATIONS. The chief indication for administration of tranquilizing drugs is the presence of anxiety manifested by psychomotor tension such as headache, backache, restlessness, irritability, fatigue, undue nervousness, difficulty in concentration and insomnia (Goldstein[13]). Tranquilizers often yield poor results in obsessive compulsive patients, in conversion hysteria, in hypochondriacal and depressive reactions. In such cases the anxiety is usually fixed either on an organ or a situation, or perhaps it is persisted in because of secondary gain.

If the anxiety is "free-floating" and is not attached, and if it has produced disorganization to the point of psychotic break, then tranquilizing drugs are not only indicated, in such cases they are mandatory. Actually, the patient should not be tranquilized but rather "normalized." Ataractic drugs, properly administered, should produce a detached serenity or a state of being without confusion; hence, peace of mind. This, however, must not be pushed to the point where the patient underestimates his danger or loses his power to combat it. All too frequently the patient is tranquilized into a serenity which detaches him from his responsibilities and his obligations so that he cannot meet the demands of his immediate environment.

The spectrum of anxiety is so broad, ranging from neurotic tension through emotional disorders to frank psychoses, that frequently indications for specific tranquilizing agents are relatively clear-cut. Thorazine may be the drug of choice in the functional and organic psychoses, especially those characterized by excitement, agitation, psychomotor hyperactivity, and assaultiveness. Reserpine likewise is effective in this group of patients. For the acutely disturbed patient, either with manic or catatonic excitement, and in the alcoholic and drug addicted patients, Sparine has been favored. Frenquel may be of use in the acute hallucinatory reactions, in the senile dissociation state, in postoperative psychoses and following excessive alcoholism. Pacatal may be of some value in this group of severe psychoses.

When anxiety is the presenting symptom as in psychoneurosis, it may improve, temporarily, with Meprobamate, or Compazine, or Trilafon, or Vesprin, or Ultran. In psychosomatic conditions such as gastrointestinal upheaval, dermatitis, allergy and possibly in cardiovascular disease with psychogenic overlay, these agents may be beneficial. Because of its muscle relaxant properties, Meprobamate is especially desirable for the associated neuromuscular tension-states. In temporary emotional stress as in over-

whelming grief, Atarax may be the drug of choice. But under all circumstances where any of these tranquilizing agents are prescribed, they must be subject to close clinical supervision. Otherwise, treacherous side-effects may overtake the patient and indirectly harm the physician.

TOXICITY. As rosy as the psychopharmacologic future may appear, the indiscriminate use of tranquilizers, ataractics, happiness tablets, peace potions or pills for the soul is mentioned only to be castigated because all of them are potentially toxic, either organically or psychologically. Self-medication with these agents can be a very dangerous form of self-indulgence.

Dickel and Dixon[7] studied the effects of tranquilizing drugs on 8,200 patients in whom anxiety was the chief finding. In 1,700 "normal" cases, serious problems were created by the tranquilizing drugs and in 1,827 abnormal patients, the emotional illness was aggravated by the medication. Nevertheless, the advertising campaign sponsored by the manufacturers of tranquilizing drugs in medical journals, on the radio, TV and in the lay press has become so bold and blatant that patients demand tranquilizers at the drop of a hat (Whiteside[33]). Thus, the physician is caught between the devil and the deep sea, and the tranquilizing agents have become a serious threat to the sound principles of medical practice.

TABLE 1.—TRANQUILIZING DRUGS

ORGANIC SIDE EFFECTS

Anorexia	Lactation
Convulsions	Menstrual Irregularities
Dermatitis	Midbrain Syndrome
Dizziness	Muscular Symptoms
Drowsiness	Nasal Stuffiness
Edema	Parkinsonism
Eye Symptoms	Ptyalism
Fatigue	Reduced Resistance to Intercurrent Disease
Flushing of Skin	Thirst
Gastrointestinal Symptoms	Toxic Syndrome
Generalized Tremulousness	Urinary Frequency
Hypotension	Voracious Appetite
Impotence	

As reported by Kline, Barsa and Gosline.[22]

TABLE 2.—TRANQUILIZING DRUGS

PSYCHOLOGICAL SIDE EFFECTS

Agitation	Nightmares
Anhedonia	Restlessness
Depression	Retardation
Eroticism	Suicide
Insomnia	Turbulent Phase
Lethargy	Withdrawal Syndrome

Kline, N. S., Barsa, J. and Gosline.[22]

At a symposium held under the auspices of the American Association for the Advancement of Science[17] entitled "Tranquilizing Drugs," some 25 organic and a dozen psychological undesirable side effects were reported, as shown in Tables 1 and 2. While space does not permit discussion of each item, a few remarks on unusual reactions to tranquilizing agents may be in order. Fortunately, the midbrain symptom seldom occurs but when it does appear it is characterized by hyperpyrexia, ocular palsies, decerebrate movement and other symptoms of brainstem intoxication. Parenthetically, agitated mental defectives are particularly prone

to develop such manifestations when given drugs to induce serenity.

Perhaps the most insidious of the side effects of tranquilizers is their action in lowering resistance to disease. If concurrent infection be present, the patient on tranquilizers would then require more vigorous therapy and more astute clinical management (Hollister[18]). For instance, the pneumonia patient will need larger doses of antibiotics in the presence of concomitant ataractic medication. The chronic cardiac treated with tranquilizers more frequently develops cardiac decompensation (Marley and Pare[23]). Coma in "tranquilized" diabetics is more precipitous and more profound (Hollister[19]). Patients who are bed-fast and who receive tranquilizing drugs frequently develop marked trophic ulcers of the heels, which in turn are recalcitrant to therapy. Thus it appears that tranquilizers, to some extent at least, impart an inability to cope with stressful physiologic situations (Kline, Barsa and Gosline[22]). Jaundice, exfoliative dermatitis and agranulocytosis are three additional warning signs of vital importance (Gambescia *et al.*[11], Kelsey *et al.*[21], Sussman and Sumner[31], Woldman and Fishman[34]).

Of the undesirable psychological effects, tranquilizers may induce a belle-indifference with no concern for standard values. If a patient cannot concentrate he cannot focus on his environment and he may appear to be somewhat dazed and confused. Or conversely, if the drug is suddenly discontinued, it may precipitate withdrawal-symptoms so that the patient regresses to typical schizophrenia (Schroeder and Perry[29]).

However, in approximately an equal number of patients in whom medication is continued, lethargy gives way to restlessness which is extreme and exhausting and may in turn be followed by agitation and mental aberrations (Muller *et al.*[26]). This turbulent phase manifests itself by extreme psychosis characterized by irritability and irrationality, by "acting out" and general lack of awareness of physical danger, often resulting in accident or injury proneness (Hall, Jackson and Swain[15]). "Anhedonia" means a lack of feeling in which the patient's attitude and outlook resemble that of a vegetable or a jelly fish. This is a rather poor bargain in exchange for normal tension. Furthermore, if the patient is depressed or has a history of depression in his background or in his family, the tranquilizers frequently make him more depressed and may force him over to frank psychosis and even suicidal endeavor.

Reserpine inhibits the sympathetic system via the hypothalamus. When this drug is given in over-dosage or in recommended strength over too protracted a period, hypotension, bradycardia, myosis, somnolence, altered sexual desire and increased appetite, diarrhea and even gastrointestinal hemorrhage may occur. Furthermore, reserpine can induce lactation in the non-pregnant female and thus initiate undesirable social implications.

The derivatives of phenothiazine (chlorpromazine, promazine, pecazine and prochlorperazine) in over-dosage will produce extra-pyramidal symptoms of blurred visison, dysarthria, dysphagia, ataxia, postural hypotension, nausea and vomiting (Schneider and Clark[28]), hypotonia, weakness and fatigue, tremors and even convulsive seizures with loss of bowel and bladder control. Since these drugs also have direct effect on the hypothalamic centers, they may initiate decrease in basal metabolic rate, hypothermia, increase in appetite with marked gain in weight, somnolence, change in sexual desire and parkinsonism (May and Voegele[24]).

Of the nonphenothiazine derivatives

meprobamate is the most popular either in the form of Miltown or Equanil. The parent substance in each case is mephenesin which is a mild muscle relaxant with some tranquilizing action. Meprobamate relaxes voluntary muscles, is anticonvulsive and is effective in behavioral changes because it blocks multineuronal pathways. This drug has selective action on the thalamus and apparently does not affect the hypothalamus or the limbic area of the brain or the cerebral cortex, except in extremely large doses. Unlike chlorpromazine and reserpine, meprobamate has no effect on the autonomic nervous system. About 90% of chronic alcoholics are sedated by this drug, often combined with small doses of chlorpromazine or azacyclonol, which is Frenquel (Travis[32]). About 30% of patients with involutional depression are benefited by meprobamate, which is said to be the drug of choice for the release of tension, anxiety and insomnia. It enjoys widespread popularity in the treatment of emotional disturbances in private practice but it has its hazards, notably the dangers of addiction (Correspondence[4], Ewing and Fullilove[9]) and intoxication (Council on Drugs[1], Shane and Hirsch[30]).

The reactions to meprobamate are minimal, about one half of one per cent, but include urticaria, maculopapular eruptions, angioneurotic edema, nonthrombocytopenic purpura, mild gastrointestinal symptoms and drowsiness. These side-effects are transient and mild and are reversible upon withdrawal of the drug. However, prolonged administration, overdosage, or covert self-administration of meprobamate may produce headache, diplopia, vertigo, syncope, fever and paradoxical excitement manifested by emotional instability, undue nervousness, jitters and a feeling of being "let-down." Parenthetically, some patients on this drug develop euphoria and convince themselves that 3 tablets 3 times a day will help them 3 times more than one tablet 3 times a day. Hence, they deliberately (though mistakenly) self-administer the drug to excess. Six 400 mg. tablets will produce a bizarre feeling of intoxication and the clinical picture of "drunk on meprobamate."

In a controlled clinical study of meprobamate habituation, 35 out of 47 patients showed staggering gait and inability to stand or walk without falling (Haizlip and Ewing[14]). Forty-four of these 47 patients experienced the abstinence syndrome upon withdrawal of the drug characterized by insomnia, vomiting, tremors, muscle twitching, overt anxiety, anorexia and ataxia. In one-fifth of the patients, the picture of hallucinosis resembled delirium tremens and in 3 patients grand-mal seizures developed upon withdrawal of the drug. In any event, meprobamate should never be combined or authorized with the use of alcohol, in spite of the popularity of "Miltini" among certain overt extroverts in show-business.

Benactyzine (Suavitil) is an atropine-like, anticholinergic compound which is spasmolytic. It has 3 times the action of quinidine on cardiac muscle and it is a local anesthetic with almost as much activity as that of cocaine. This drug is said to block selectively certain pathways in the hypothalamus, which may explain why patients taking benactyzine show less reaction to emotional stimuli. It not only raises the pain threshold but also the threshold of fear and thereby is said to abolish tension, or at least prevent its development. This dual action has been termed "dephobic." Shortly after ingestion of this medication, feelings of detachment and general apathy appear which may lead to depersonaliz-

ation and amorality. Large doses from 4 to 8 mg. blunt the sensibility, induce loss of concentration and a hesitancy in speech with a certain amount of thought-blockage. In addition to this mental relaxation, there is also muscle relaxation to the extent where the knees feel like jelly and the feet seem glued to the floor, so that the patient would rather remain in a wallow than get up out of the muck. If overdosage continues, the victim may readily develop ataxia, vertigo and even collapse. Psychotic patients are not benefited by or from this drug, even though it is said to have low toxicity.

The so-called "low toxicity" of any tranquilizer may represent a psychological hazard. In other words, the anxious patient may become more anxious because he no longer feels anxious while taking a tranquilizer! He worries because of his lack of worry and he feels that there is "a catch in it somewhere." In short, natural anxiety may be a normal defense mechanism and therefore have virtue in its own right. When anxiety is suddenly and completely removed by the administration of a tranquilizing agent, the patient promptly finds himself at sea and utterly confused by a situation with which he cannot cope. He, therefore, must substitute a more normal defense mechanism, if he can summon one, or fall flat on his face.

Hostile patients who are filled with chronic anger do not do well on tranquilizers, nor do patients dominated by obsessional mechanisms. Sudden depersonalization may induce a fear of going mad. Latent homosexuals occasionally become active or even hyperactive in an overt manner after the ingestion of tranquilizers.

Conclusion. Such then are some of the treacherous aspects of tranquilizing drugs. Small wonder that the American Psychiatric Association recommends that tranquilizers should not be employed unless a physician first sees the patient and establishes the facts.

Finally, equanimity, tranquility and peace of mind are found in oneself and not in a bottle on the pharmacist's shelf (Davis[5]). It may be true that our civilization is bungling through a period of idealogical controversy, but what civilization in human history has not floundered from one crisis to another? If crisis produces tension (or *vice versa*), then this tension should be used constructively to overcome the crisis so that the drive to self-transcendency may become a positive force for good.

Anxiety is like smoke, which precedes fire. The fire may be used to great advantage in our daily lives as a source of celestial energy. If it rages out of control, a conflagration ensues. Tranquilizers may be prescribed judiciously to prevent or put out smouldering brush fires but they should not be called upon to quench a forest fire; neither should they be employed to stifle completely anxiety from which the warm, blue flame of ambition and accomplishment is lit.

Peace of mind, like the pursuit of happiness is a transitory affair. It is not an end unto itself. It should be sought primarily as a means to insure our ability to live and to keep on living, to face the present and the future with enthusiasm and not to mourn the past. In 1663 the poet John Milton[25] most aptly wrote: "The mind is its own place and in itself can make a Heaven of Hell, a Hell of Heaven."

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Tranquillisatores Traitori

SUMMARIO IN INTERLINGUA

Es castigate le uso promiscue del moderne agentes psychopharmacologic de "tranquillitate del anima." Criterios es proponite que determina quando le uso de un tranquillisator chimotherapeutic es indicate e que defini le effectos que illo debe producer in le caso individual.

Le autor se declara de accordo con le recommendation del Association Psychiatric American secundo le qual tranquillisatores non debe esser usate si le patiente non ha vidite un medico capace a establir le factos in le caso particular.

In su conclusion le autor dice: Equanimitate, tranquillitate, e serenitate del anima es a trovar in le profundor del personalitate individual e non in un bottilia in le officina del apothecario. Il es possibilemente ver que nostre civilisation

se move sin ben formulate objectivos a transverso un periodo de controversia ideologic. Sed qual civilisation in le historia del humanitate differeva in isto ab le nostre? *I.e.*, qual civilisation non progredeva per multiple essayos e errores ab un crise al proxime? Si crises produce tensiones (e vice versa), alora le energia de tal tensiones debe esser usate constructivemente in le resolution del crises, de maniera que le impulso del humanos de transcender se mesme va devenir un fortia positive in le servicio de objectivos de alte valor.

Le anxietate es como le fumo que precede le fumo que precede le foco. Le foco pote esser usate a grande avantage in nostre vita diurne como fonte de energias celeste. Sed si le foco se inragia e escappa al dominio rational, le consequentia es un conflagration. Tranquillisatores pote esser prescribite judiciosemente pro prevenir o extinguer un foco al margine del foresta, sed illos non debe esser empleate in combatter un incendio de invasion general. E etiam: il non es juste usar tranquillisatores pro reprimer completemente omne tracia de anxietate, proque il es anxietate ab que se deriva le calide flamma clar del ambition e del successo.

Le tranquillitate del anima—como le cerca del felicitate—es cosa transitori. Illo non es un objectivo e non un valor per se. Illo debe esser cercate primarimente como un medio que mantene nostre capacitate de viver e de continuar viver, de tener nos facie a facie con le presente e con le futuro, plen de enthusiasmo e sin regretto pro le cosas que es passate. In le anno 1663 le poeta John Milton scribeva aptissimente: "Le regno del mente es intra le mente. Intra se, le mente pote cambiar Inferno in Cello in Inferno."

(Continued from page 157)

cos que es positive pro coagulase debe esser typate per bacteriophagia pro identificar le racia prevalente e pro traciar su origine possibile. Depost circa 1955, staphylococco typo 80/81 es le plus frequente causa de epidemias hospitalari, sed certe altere typos ha etiam essite trovate responsabile pro le production de epidemias.

In combatter tal infectiones, un mesura del prime importantia es le stricte isolation del patientes inficite e le suspension de membros inficite del personal. Altere mesuras debe esser determinate localmente per le hospitales individual. Le Committee pro Infectiones intra le hospital debe esser responsabile pro le determination de tal mesuras e debe haber le autoritate pro insister que illos es executate. Le therapia routinari de infectiones in patientes e membros del personal non require le uso de antibioticos. Le racia epidemic de staphylococco 80/81 non es plus resistente contra germicidas que altere staphylococcos. In le ultime analyse, le evalutation del efficacia de un germicida applicate al muros, solos, e coperturas de lana depende del effecto que illo exerce super le incidentia de infectiones in le hospital. Il es a sperar que un officio governamental de hygiene va interprender tests del efficacia de ille preparatos, tanto in le laboratorio como etiam in applicationes practic. Informationes additional es requirite ante que on pote reguardar como significative le presentia de staphylococcos in un inanimate reservoir del ambiente.

Infectiones staphylococcal de acquisition nosocomial va probabilemente esser un problema de longe permanentia, proque le racias epidemic passa al publico in crescente numeros. Isto significa que le publico va continuar a re-disseminar staphylococcos in le hospitales.

MEDICAL ASPECTS IN THE CONTROL OF HOSPITAL ACQUIRED STAPHYLOCOCCAL INFECTIONS*

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There has been some debate as to whether or not there really exists today a problem of hospital acquired staphylococcal infections. Attempts have been made to compare today's incidence of surgical wound infections with that of 10 or 20 years ago. The figures for today's wound rates are being compiled from an active study of the patients and are thus quite accurate. However, the figures for one or two decades ago can be obtained now only from a chart review and because of the inherent inaccuracies of hospital charts are not reliable for valid comparison. Hence this question remains unanswered.

Whether or not this is a new problem is rather academic and not significant to the hospital which finds itself in the midst of a small epidemic of hospital acquired infections. Such a hospital is more interested in how to cope with this situation which has so suddenly appeared.

One of the first steps involved in dealing with the situation is to determine the magnitude of the hospital's problem. Some of the first reports on this subject concerned epidemics localized to nurseries (Colbeck[5]), or surgical units (Blowers *et al.*[4]) and some epidemics still appear to be so confined to one service. But there are reports such as ours from Temple University Medical Center (Schreck *et al.*[6]) where all services were involved with the infections at one time. A study must be undertaken, therefore, to determine the extent of the problem in a given hospital and this, of course, becomes one of the tasks of the Committee on Infections recommended by the Joint Commission on Accreditation of Hospitals.

The extent of the problem can be determined for those infections occurring in the hospital by having the bacteriologist bring to the attention of the committee the names of all patients from whom a coagulase positive staphylococcus has been isolated. The status of each of these patients is determined by one of the committee members who then reports his findings to the committee. If the patient were found to have an infection, the committee classified the type of infection for tabulation. This method of course is only useful where the attending staff is diligent in routinely culturing all known and suspected infections.

An alternate method to make the infections known to the committee is the one of requiring the attending physition to report infections to the hospital administrator; but this method usually falls short of the goal. Another method, used in Britain (Shooter *et al.*[10]), is a wound book in which, for each patient, a postoperative entry of "yes or no" must be made with regard to the appearance of wound suppuration. This is an excellent device to make surgical wound infections known, but will not bring to attention the

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abscesses or pneumonias occurring in nonsurgical patients.

Workable methods can be devised to make known all infections developing while the patient is in the hospital. But it must be appreciated that these figures will not reflect the true incidence of hospital acquired infections because some of the infections appear after discharge of the patients, for example, postpartum breast abscesses appear about 3 weeks after delivery and many infections of the newborn appear only after discharge. So a follow-up survey in these areas is required for a true incidence of infections. For this follow-up survey, some workers prefer the printed form which the postpartum mother is to return by mail so many days after delivery, while others prefer the phone call interview or home visit.

We feel that these infections must be studied on a hospital basis rather than a departmental basis. For this reason, it has been suggested that the Committee on Infections should consist of representatives of each of the clinical departments as well as a representative from bacteriology, administration, nursing, and housekeeping. Such composition of the committee should make for better understanding and cooperation of the entire staff. There then should not exist the hypothetical situation in which the nursery is aware of its problem and is fighting it while the surgical service or the medical service has equally as bad a problem but has not recognized it and thus is doing nothing about it.

At this point we might consider what should be done now assuming an epidemic is present. Many control measures will be invoked and many of these will have to be devised as local conditions dictate. But before considering the control measures, it should be indicated that merely tabulating figures as to the number of infections occurring with coagulase positive staphylococci is not sufficient in defining the situation. An attempt should be made to detect what staphylococcus is the main offender in the epidemic.

The best method available today for actually identifying a given staphylococcus is bacteriophage typing (Blair and Carr[2]). This technique has revealed that the staphylococcus of main concern throughout the world today is the type 80/81. This strain has been variously designated by us as type 42B/52/81 and by others as 42B/44A/47C/52 and 42B/44A/52. This strain in the past 3 or 4 years has gained supremacy replacing the group III phages which were previously most commonly found in hospital acquired infections (Blair and Carr[3]). This type 80/81 is the strain which accounted for 63% of the 323 hospital related staphylococcal infections we experienced in the first year of our study, and which today is still accounting for the majority of our infections.

The U.S. Public Health Service in joint sponsorship with the National Research Council held a National Conference on Hospital Acquired Staphylococcal Disease in September. At this meeting it was agreed that bacteriophage typing should not be undertaken by the individual hospitals, other than those already so engaged, because of the technical difficulties concerned. Hospitals faced with an epidemic, however, should have the advantage of having bacteriophage typing done on their isolated staphylococci. Such service will be available from regional typing centers, some of which are already established and which will be supplied with phages by the Communicable Disease Center of the Public Health Service.

The management of a given patient

with staphylococcal infection will not be influenced by the knowledge of the phage type of his organism. But phage studies are important in attempting to trace the source of the epidemic. It should be noted that the small hospital might be the very one which, with the aid of typing, may determine the source to be a healthy nasal carrier, whereas the large medical center, where so many personnel are rotated so frequently, might never be able to do this. One may say, "Well, my laboratory cannot do phage typing, but we can do antibiotic susceptibility testing. Therefore I will use the antibiotic pattern to trace the offending organism." To this I must state emphatically that the antibiotic pattern does not distinguish between phage types and, therefore, is not a substitute for phage typing. Thus it becomes highly desirable for small hospitals as well as large ones to take advantage of phage typing.

While knowledge of the phage type of a patient's organism will not influence his management, it is in some measure useful in predicting what the patient and his family may anticipate. If type 80/81 is the organism, the patient might experience what some of ours have, namely, recurrent infections for upwards of a year and passage of the organisms, with resulting infection, to one or all of the members of the household without regard for age or sex. It should be noted that while type 80/81 had been most prominent in causing such sequences as this, there are a few other types which have also caused hospital infections and have followed to the home and the community.

Having defined the extent of the problem and considered the offending organism, what now are the control measures to be used? As I have indicated, many of the control measures must be decided upon locally as determined by a reappraisal of the existing conditions and techniques of the institution. The Committee on Infections should be charged with the responsibility of this reevaluation and supported with the authority to effect the required changes.

A number of control measures will be rather uniformly invoked without study. Foremost among these should be the very obvious but often ignored strict isolation of the patient with staphylococcal infection. Ideally, I think that this should be carried out in an isolation unit which would keep the organism more confined to one area of the hospital and in which the patients would be cared for by a few select personnel highly skilled in isolation technique. But it appears that this is luxury that most hospitals, including our own, cannot afford.

The next most obvious thing to do is to remove personnel from duty when they are suffering active staphylococcal infections. In the first year of our study, 99 of our personnel developed infections, 80% of which were caused by type 80/81. This is an extremely hard problem to meet because so many of the personnel will continue to work without making it known that they have a buttock or axillary abscess. As we have pointed out, the actual modes of transmission of the staphylococcus to the patient have not yet been determined, but it cannot be denied that a patient's contact with an infected doctor or nurse is a very important possibility. A system to detect personnel infections should be established.

The role of the healthy nasal carrier in transmitting the organism to the patient is a debated point. There are a few reports that claim that an epidemic was traced to a healthy nasal carrier; as I indicated, this may possibly best be done in a small institution.

There is also a report in which a nurse nasal carrier of type 52A was working in a nursery which experienced no infant infections until a new nurse with a face abscess caused by 52A came on duty and then the infants became infected (Barber and Burston[1]). These instances may support the suggestion that has been made that there are "dangerous carriers," but what criteria will place one in this category are not clear.

I did not attach much significance to nasal carriers in our situation because we had only 11 carriers of type 80/81 among our staff of 640 who were surveyed. This number was far overshadowed by the 99 of our personnel who had active infection. While I did not entirely dispense with the importance of the nasal carrier, I stated that more likely most of our transmission was via infected personnel (Schreck *et al.*[6]).

The National Conference on Staphylococcal Disease agreed that periodic nasal surveys of nursery personnel should be made and carriers of known epidemic strains removed from duty until free of the organism. Nasal surveys of other personnel are not recommended until an epidemic is present and the nasal carriers of the epidemic strain should then be excluded from surgery. Claims have been made that the organism can be eliminated from the nose of a carrier by various forms of therapy, but I think more study of this is required before this can be recommended as a worthwhile procedure.

We feel that most of the patients with staphylococcal infections should be treated conservatively with incision and drainage performed at the proper time[6]. Antibiotics are not part of our therapy for the usual abscess because in most instances they do not influence the process. However, antibiotics may arrest an incipient abscess and in cases like mastitis may prevent the progression to actual abscess formation. The plea for more discriminant use of antibiotics is universal, but I have serious doubts that this will be accomplished within a hospital by any measure short of actually prohibiting the use of certain of the newer antibiotics. If a simple plea is made to curtail the use of a given drug, I anticipate that each physician will say "I'll use it just this once" and when this is multiplied by the number of staff men there has been no curtailed use. An antibiotic control officer may be the only answer to this problem.

At the recent staphylococcal conference, it was agreed that the routine prophylactic use of antibiotics in hospitalized patients was highly undesirable. We have actually condemned this practice in both the pre- and postoperative periods with the possible exception of the standard preoperative preparation of the bowel and in surgery for tuberculosis. We do not condone prophylactic antibiotics in surgery because the drugs so employed are usually penicillin, streptomycin and tetracyclines and the hospital staphylococcus is resistant to all three. Therefore the opportunity is provided for an almost pure flora of this organism to develop in or on the patient.

One area in which I would subscribe to the prophylactic use of antibiotics, indeed perhaps even think it mandatory, is the newborn nursery experiencing an epidemic, and here it may be argued that this is therapy rather than prophylaxis. While erythromycin, chloramphenicol, and kanamycin are some of the drugs which have been so employed, the antibiotic to be used in any given nursery will have to be determined at the time. While erythromycin was useful in Shaffer's nursery[6], it was not in ours because from the beginning our type 80/81 staphylococ-

cus was resistant to erythromycin. When we were considering the use of a drug in our nursery, novobiocin was available but not yet on the market and for that reason we did not use it. It is conceivable that under circumstances worse than prevailed in our nursery, a soon-to-be-released drug might have to be employed.

It is evident that there are many facets to the control of staphylococcal infections. Until we understand the epidemiology of this organism, our control measures will remain empiric. Very fundamental to our understanding of the epidemiology is a knowledge of the virulence of the organism obtained from various sources. We have no good way to test virulence today, but we would like to know what the virulence of the organism is when it is recovered from the air and what is the virulence of this same type 80/81 which has been dried on a blanket for 4 months; what is the virulence of the strain when present in the nose of a healthy nasal carrier and is it the same in all nasal carriers? When these matters are known, perhaps we can disregard some of these reservoirs.

The actual importance of the airborne organism is not known. One can always assume that wounds become seeded with airborne droplet nuclei at the time of surgery, but this cannot be proved. My studies on air sampling, using a sieve sampler, revealed that the epidemic strain of staphylococcus is very infrequently recovered from the air, which is in contrast with several reports on air studies. In fact, only 32 coagulase positive staphylococci were isolated from 485 cubic feet of air sampled from various areas of our hospital (Schreck and Margarida[7]). Of these 32 staphylococci, only 16 were the epidemic strain, which meant that the airborne particle carrying the epidemic strain was present in a concentration of only one particle per 30 cubic feet of air. No staphylococci were isolated from our operating rooms. The patients who most readily contaminated the air in this study were one with a colostomy and furunculosis and another with a tracheotomy. These certainly are the types of patients to be isolated.

Blankets have also been considered a potential reservoir of the organism and I agree that they may be. Several reports indicate that following laundry, blankets may bear as many as 1600 to 2000 bacterial colonies per sampled area, practically as many bacteria as were present before washing. I have not been able to confirm these high counts following our blanket laundry process (Schreck and Piper[8]). By sweeping a blood agar plate over one square yard of our blankets immediately after being dried, I have demonstrated only 0 to 40 colonies per plate; and in a study of 100 blankets (either wool or 50:50 wool and cotton) over a 3-month period only one colony of a coagulase positive *Staphylococcus aureus* was detected. Our laundry process is apparently a standard one used in many hospitals. But one difference is that we dry our blankets in a steam-heated (160° F.) chamber for 20 minutes while many laundries hang their blankets to dry over night. The drying chamber does not, however, account for our extremely low counts, because blankets we have dried on a rope overnight have never had the high counts reported by others.

Some manufacturers of germicides, air conditioners, paints, and floor waxes are assuming that the inanimate reservoirs are extremely important in this problem. Hospital administrators and infection committees are being flooded with new and often expensive products to combat the problem. In this regard, I will only say that the National Con-

ference on Staphylococcal Diseases has recommended to the Surgeon General of the Public Health Service that some federal agency, and state agencies if possible, be designated to pass on the merits of these new compounds including the residual acting germicides and then to determine if they influence in any way the actual infection rates in field trials. To be sure, some of these materials work in the laboratory, but what they do in hospital use must be determined. It does not seem reasonable that a hospital should expend much effort and money in attacking the inanimate reservoir which is of questionable importance when an undetected infected person remains on duty in that environment and passes his organism directly to the patient, not via the germicide treated floor, blanket, or wall.

An extremely important point that must be understood is that the staphylococcus of the epidemic strain is no more resistant to germicides than is the ordinary staphylococcus. In other words, even though the organism is resistant to several antibiotics, this resistance is not carried over to germicides. So if a new product is sold to kill the "resistant staphylococcus," the phrase "resistant staphylococcus" is out of context, a half truth, and conveys a false impression.

The question is asked, if we are seeing more hospital acquired infections today, why? The answers frequently given are: more radical types of surgery are producing patients with greater susceptibility, adrenal cortical steroid therapy is reducing the resistance of patients, and the elderly patients are by reason of their age more susceptible. I am not sure that our series bear out these suggestions. An alternate explanation is that the organism we are dealing with today has a greater capacity of transmissibility in numbers great enough to cause infection and while this may be construed to mean that the organism is more virulent, I will not use that term until we can test for virulence. Of all these possibilities, I subscribe to the latter, because it can not only account for why our patients are becoming infected but can also account for why a large group of student nurses in the prime of life becomes infected.

Finally we might ask how long we might expect to have this problem in our hospitals. This of course is hard to predict, but it might be said that since type 80/81 is going home with patients this is now becoming a community problem. This is reflected in the fact that in our first year of study, 16% of the patients admitted to the hospital because of staphylococcal infections were already infected with type 80/81. In the second year this figure rose to 28%. So this means that the community is going to keep the hospitals supplied with the organism. And since there has been such widespread distribution of this staphylococcus, I feel this will be a long term problem on a national scale. Even though the community reseeds the hospital, it does not follow that the number of hospital acquired infections will remain at a given high level. We were fortunate that in our second year we had 122 fewer infections than in our first year. Most of this reduction occurred in the category of clean surgical wounds.

Perhaps our real salvation in this problem rests in the information which will come from a restudy of the basic fundamentals of the staphylococcus and the many aspects of the host-parasite relationship. It has been recommended to the Surgeon General that a good portion of the over one million dollars appropriated by the last session of Congress for the study of staphylo-

coccal disease be channeled to this basic and sorely needed research.

Summary. When a hospital is confronted with hospital acquired staphylococcal infections, the extent of the problem should be determined by tabulating all infections related to hospitalization including those occurring in the immediate period following discharge of the patient. When an epidemic is present, all isolated coagulase-positive staphylococci should be bacteriophage typed to find the prevalent strain and to trace its possible source. Since about 1955, type 80/81 staphylococcus has been the most frequent cause of hospital epidemics but a few other types have also been found to produce epidemics.

Paramount in successful control is strict isolation of infected patients and removal from duty of infected personnel. Other control measures must be decided upon locally by a given hospital. The hospital's Committee on Infections should institute these control measures and have the authority to enforce them. Routine therapy of patient and personnel infections does not require the use of antibiotics.

The epidemic strain of staphylococcus 80/81 is no more resistant to germicides than is any other staphylococcus. The final assessment of the value of a germicide applied to walls, floors, and blankets lies in its effect on the infection rate in a hospital. It is hoped that a governmental health agency will conduct laboratory and field trials on these preparations. More information is required before significance can be attached to the staphylococci in the inanimate environmental reservoir.

Hospital acquired staphylococcal infections will probably be a long-term problem, because the epidemic strains are passing to the community in greater numbers. This means the community will continue to reseed the hospitals with the staphylococci.

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SUMMARIO IN INTERLINGUA

Aspectos Medical In Combatter Infectiones Staphylococcal De Acquisition Nosocomial

Quando un hospital se trova confrontate con le problema de infectiones staphylococcal acquirite al hospital, le magnitude del problema debe esser determinate per le tabulation de omne infectiones relationate al hospitalisation, incluse illos que occurre durante le periodo immediatemente post le dimission del patiente. Quando le situation es illo de un epidemia, omne le isolate staphylococ-

(Continued on page 150)

THE DIAGNOSTIC AND THERAPEUTIC VALUE OF THYROTROPIC HORMONE AND HEAVY DOSAGE SCINTIGRAMS FOR THE DEMONSTRATION OF THYROID CANCER METASTASES*

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Our program of treatment of cancer of the thyroid[6,7,8], ranging over a period of 6 years, has shown that 78% of our cases with metastases collect I^{131}. This figure can be attributed in great part, to the use of a heavy dosage scintigram study (1 to 2 millicuries tracer dose) after thyrotropic stimulating hormone administration. The purpose of this paper is to illustrate the technique and to indicate the various elements involved in its success, and to stress the lack of reliability of the 24-hour I^{131} uptake and the 72-hour excretion studies when used alone.

Methods. The Reed Curtis Scintiscanner is used in all our studies. After surgical removal of all resectable thyroid tissue, cancerous and normal, the patient received 10 units of thyrotropic stimulating hormone‡ intramuscularly daily for 5 to 7 days, after which 1 to 2 millicuries (tracer dose) of radioactive iodine are given by mouth. Total body scanning and routine scintigrams of the neck, chest and metastatic sites are then done; if there is any evidence of collection of I^{131} by residual tissue in the neck or metastatic sites, a therapeutic dose of I^{131} (40 to 100 millicuries) is given. Seven days later, a repeat scanning and scintigram is taken to establish the precise collection of the isotope with the larger dose. In the known metastatic cases, if no collection of I^{131} was obtained with the tracer dose, a therapeutic dose is given to ascertain if some pick-up might be found with the greater amount of I^{131}. The 24-hour uptake of I^{131} and the 72-hour excretion studies were done with a dose of 100 microcuries of I^{131}.

Immediately after the initial radioactive iodine studies are completed, all patients are started on dessicated thyroid U.S.P., or sodium-levo-thyroxine medication in gradually increasing doses until the patient is euthyroid, as indicated by a high normal protein bound iodine. The patients who receive the therapeutic dose of radioactive iodine are re-studied approximately every month, the others, every 3 to 6 months. Skeletal roentgenograms and blood counts are done at the time of each study.

Illustrative Material. The 8 illustrative cases that follow are part of the 44 cases whose clinical and pathological data have been reported (Catz *et al.*[8]).

DOSAGE OF THYROTROPIC HORMONE. *Case 1.* Increased collection of I^{131} by the administration of a greater amount of thyrotropic

Paper was presented at the meeting of the American Goiter Association in San Francisco, California, June, 1958.

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†With the technical assistance of Virginia Haste.

‡Thytropar, generously supplied by Armour Laboratories, Chicago, Ill.

stimulating hormone. S.O., a 23-year-old woman, had a total thyroidectomy and right radical neck dissection for papillary carcinoma metastatic to lymph nodes. Following surgery 10 units of thyrotropic hormone were given intramuscularly daily for 2 days (total dose 20 units). Twenty-four hours later 410 microcuries of I^{131} were given. The 24-hour scintigram of the neck as seen in Fig. 1A reveals a negligible collection of radioactive iodine in the thyroid region. A repeat study after administration of 10 units of thyrotropic hormone daily for 7 days (total 70 units) shows (Fig. 1*B*) a greater collection of I^{131} in the region of the neck. After the therapeutic dose of 100 millicuries is given, a wider spread of collection of I^{131} can be observed (Fig. 1*C*).

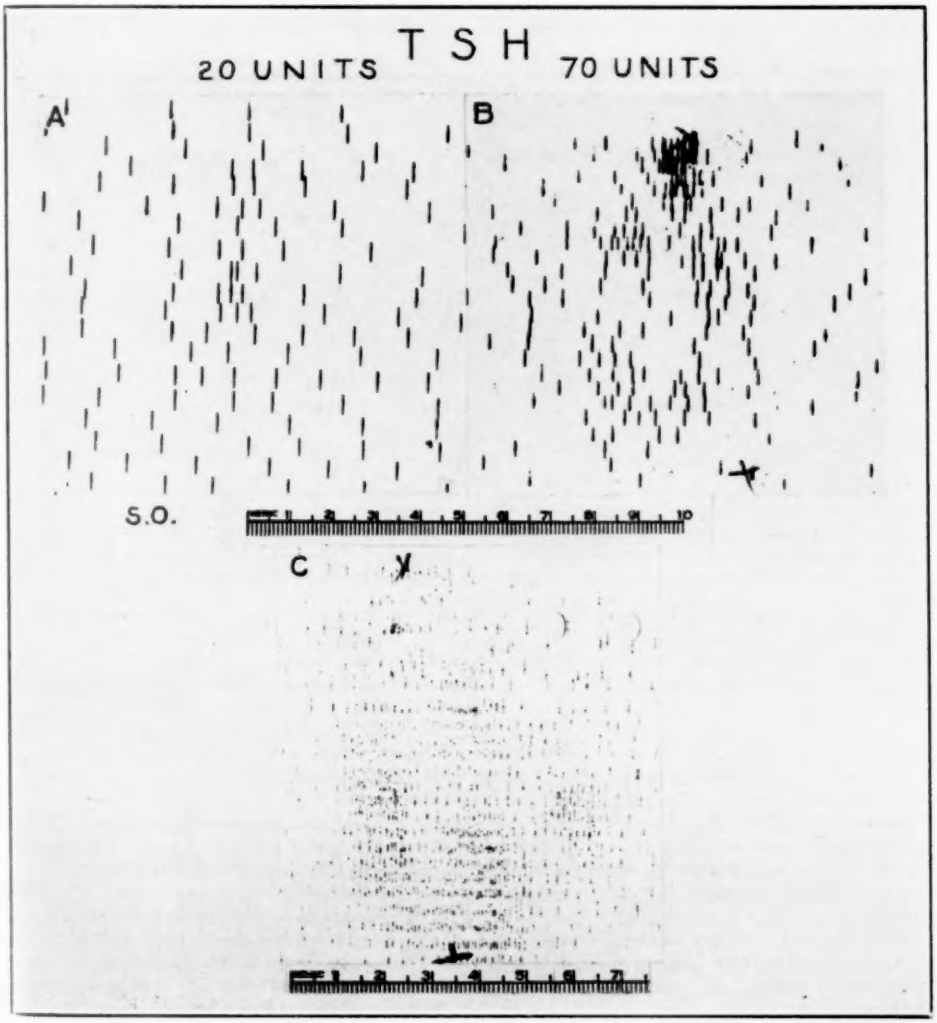

Fig. 1.—Increased collection of I^{131} by the administration of a greater amount of thyrotropic stimulating hormone. S.O. *A*. Scintigram of the neck after administration of 20 units of thyrotropic hormone. The tracer dose of I^{131} was 410 microcuries. *B*. The same, after administration of 70 units of thyrotropic stimulating hormone. Notice the increased collection of I^{131}. *C*. After a therapeutic dose of 100 millicuries, a wider spread collection of I^{131} can be observed.

This case indicates the usefulness of intensive thyrotropic stimulating hormone administration (70 units) in the detection of residual thyroid tissue.

POSITIVE SCINTIGRAM DESPITE NEGATIVE 24-HOUR UPTAKE AND 72-HOUR EXCRETION STUDIES. *Case 2.* F.B., a 25-year-old woman, had a total thyroidectomy and radical right neck dissection for a papillary carcinoma. The studies were done while the patient was taking 2 grains of U.S.P. thyroid daily. As seen in Fig. 2, after 60 units of thyrotropic stimulating hormone the 24-hour uptake was 0.12% and the 72-hour excretion was 94%. Despite these results a scintigram after 1 millicurie of I^{131} revealed collection of I^{131} in the thyroid region. This can be seen clearly in Fig. 2. We are unable to ascertain if this tissue is normal residual thyroid, or cancerous tissue.

Case 3. R.G., a 68-year-old woman, had a total thyroidectomy for a follicular and alveolar carcinoma. At the time of surgery invasion of the trachea and surrounding tissues was observed. No further surgery was done. Our studies were performed while the patient was taking 3 grains U.S.P. thyroid daily. After 70 units of thyrotropic stimulating hormone the 24-hour uptake was 0.3%, the 72-hour excretion was 90.7%. Despite these results a scintigram of the neck, after 100 millicuries of I^{131}, revealed an intensive collection of I^{131} (Fig. 3).

Case 4. J.F., 52-year-old man, in 1949 had a subtotal thyroidectomy for alveolar and follicular carcinoma. In 1952 metastases were discovered in the cervical, dorsal and lumbar spine, the left ileum and right anterior chest cage. During 1953 a total of 100 millicuries of I^{131} was given as therapy. In 1954, roentgenologic therapy was given to the lumbar spine.

Our initial studies were done in May, 1955. The patient was on 0.4 mg. of l-thyroxine daily. After 70 units of thyrotropic stimulating hormone, the 24-hour uptake of I^{131} in the neck, chest and metastatic sites, was 0.4% and the 72-hour excretion studies were 87.3%. A scintigram with one millicurie was doubtfully negative. Repeat scintigram after 100 millicuries of I^{131} showed intensive collection of the isotope in the region of the thyroid, right anterior chest and the lumbar and iliac regions (Figs. 4*A* and *B*).*

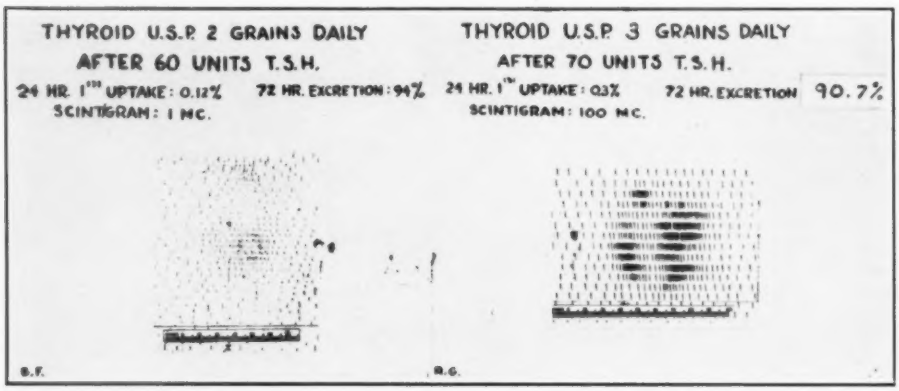

Fig. 2

Fig. 3

Fig. 2.—Positive scintigram despite negative 24-hour uptake and 72-hour excretion studies. B.F. Patient taking 2 grains of thyroid U.S.P. daily. After administration of 60 units of thyrotropic stimulating hormone, the 24-hour I^{311} uptake and 72-hour excretion studies were negative, while the scintigram with the 1 millicurie dose shows the presence of residual tissue.

Fig. 3.—Positive scintigram despite negative 24-hour uptake and 72-hour excretion studies. R.G. Patient taking 3 grains of thyroid U.S.P. daily. After administration of 70 units of thyrotropic stimulating hormone, the 24-hour I^{131} uptake and 72-hour excretion studies were negative. After 100 millicuries of I^{131}; the scintigram reveals great collection of I^{131}.

*We acknowledge with thanks the cooperation of Dr. Robert R. Commons in the successful following of this case.

Cases 2, 3 and 4 indicate that despite routine uptake and excretion studies, which would be considered negative, the scintigrams with heavy dosage were positive in all instances.

TRACER DOSE SCINTIGRAM NEGATIVE: THERAPEUTIC DOSE SCINTIGRAM POSITIVE. *Case 5.* M.P., 75-year-old man, had total thyroidectomy and left radical neck dissection for papillary carcinoma with spread to lymph nodes. At the time of surgery invasion to surrounding tissues was noticed. No further surgery was undertaken. While on intake of 6 grains of thyroid U.S.P. daily, 70 units of thyrotropic stimulating hormone were administered. As seen in Fig. 5 *A*, the scintigram after 1 millicurie was considered to be negative. After 50 millicuries of I^{131} the scintigram demonstrates (Fig. 5 *B*) collection of I^{131} in the anterior neck.

Cases 4 and 5 lend emphasis to the fact that wherever metastatic tissue exists, one should not consider a scintigram negative unless it is repeated after a therapeutic dose (40 to 100 millicuries) of I^{131}.

PERSISTENCE OF POSITIVE SCINTIGRAM AFTER REPEATED THERAPY WITH I^{131}. *Case 6.* J.G., 33-year-old woman had a total thyroidectomy and regional lymph node resection for a papillary and alveolar carcinoma, in 1949. At the time of surgery invasion of the trachea and esophagus was noticed. No further surgery was done. In 1949 roentgenologic therapy to the neck was given. In 1953 and 1954, 24-hour uptake and 72-hour excretion studies after 70 units of thyrotropic stimulating hormone administration were considered to be negative. In 1955, 1956 and 1957 scintigram studies were performed after 70 units of thyrotropic stimulating hormone were administered. On each occasion they were positive. The last of these studies is shown in Fig. 6. It can be seen that the 2 millicuries dose scintigram (Fig. 6*A*) was questionably positive, while the 25 millicuries scintigram (Fig. 6*B*) was definitely positive.

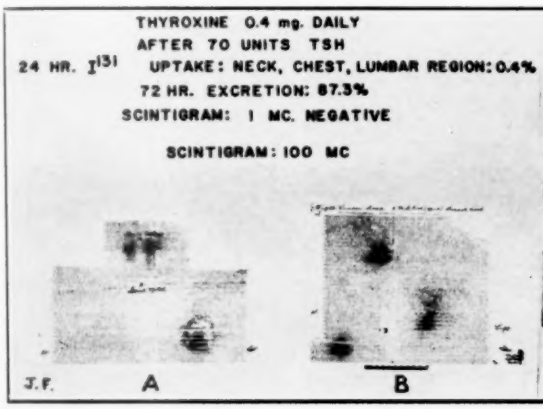

Fig. 4

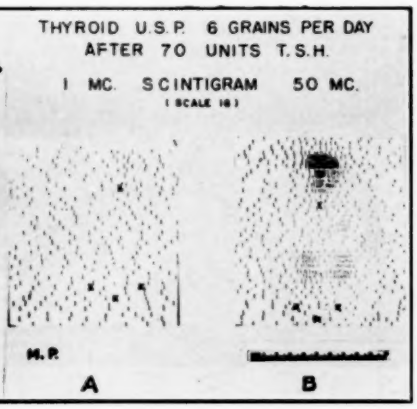

Fig. 5

Fig. 4.—Positive scintigram despite negative 24-hour uptake and 72-hour excretion studies. J.F. Patient on 0.4 mg. of thyroxine daily. After 70 units of thyrotropic stimulating hormone the 24-hour I^{131} uptake and the 72-hour excretion studies as well as the scintigram with 1 millicurie, were considered negative. Scintigram after 100 millicuries: *A.* Reveals collection of I^{131} in the neck and in the right upper chest. *B.* Collection of I^{131} is observed in the lumbar and iliac region.

Fig. 5.—Tracer dose scintigram negative: therapeutic dose scintigram positive. M.P. Patient on 6 grains thyroid U.S.P. daily. *A.* After 70 units of thyrotropic stimulating hormone, scintigram with 1 millicurie is negative. *B.* After 50 millicuries of I^{131} the scintigram reveals collection of I^{131} in the neck.

Case 6 stresses the importance of continuous testing and treatment and shows the persistent functioning of the residual tissue without change in the collection of I^{131}.

FOR SIMILAR RESULTS: SIMILAR TECHNIQUE. *Case 7.* E.B., 72-year-old woman had a total thyroidectomy for a follicular and alveolar carcinoma with capsular and vein invasion. Initial scintigram studies after 70 units of thyrotropic stimulating hormone (Fig. 7*A*) revealed collection of I^{131} in the thyroid region. Because of unavailability of a therapeutic dose at that time, repeated studies were performed at a later date. To our surprise (Fig. 7*B*) the scintigram was negative, but after the therapeutic dose (Fig. 7*C*) it showed marked collection of I^{131}. A review of the technique used showed that the initial studies (Fig. 7*A*) were done with the scale of 8 while the repeat studies used the scale of 16. This demonstrates the importance of using the same scale at all times, preferably the lower and most sensitive one.

PREOPERATIVE DEMONSTRATION OF COLLECTION OF I^{131} BY METASTATIC TISSUE PROVED TO BE HISTOLOGICALLY A PAPILLARY TYPE. *Case 8.* S.S., 70-year-old woman had a total thyroidectomy in 1947 for papillary carcinoma. In 1949 roentgenologic therapy was given. In 1954 appearance of several nodules in the thyroid region was noticed. Twenty-four-hour uptake studies after 70 units of thyrotropic stimulating hormone revealed a value of 1.3% in the left nodular area. A scintigram with 75 millicuries showed intensive collection of I^{131} over the left nodular area (Fig. 8). A left radical neck dissection was performed and the histologic diagnosis was papillary carcinoma, metastatic to lymph nodes.

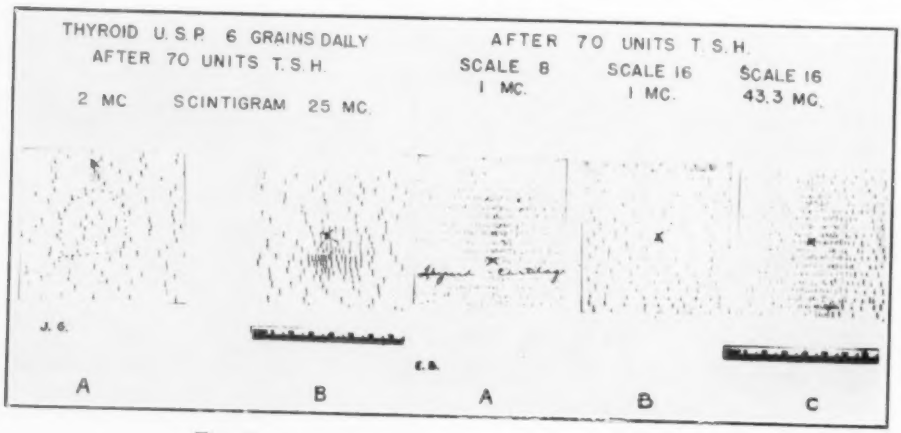

Fig. 6

Fig. 7

Fig. 6.—Persistence of positive scintigram after repeated therapy with I^{131}. J.G. In 1955 and 1956 studies after thyrotropic stimulating hormone administration revealed collection of I^{131} in the neck. The present study was done in 1957. Patient on 6 grains thyroid U.S.P. daily. After 70 units of thyrotropic stimulating hormone: *A.* Scintigram with 2 millicuries of I^{131} is questionably positive. *B.* Scintigram with 25 millicuries of I^{131} is positive.

Fig. 7.—For similar results: similar technique. E.B. After administration of seventy units of thyrotropic stimulating hormone: *A.* Scintigram with 1 millicurie of I^{131}, scale 8, positive. *B.* Scale 16 scintigram, negative. *C.* After 43.3 millicuries, scale 16 scintigram, positive. This demonstrates the importance of using the same scale at all times, preferably the lower and most sensitive one.

This case serves as a reminder that the histologic type does not decide the collection of I^{131} by the tissue.

Discussion. The use of the scintigram technique is not new (Allen and Goodwin[1], Allen, Libby and Cassen[2],

Bauer *et al.*[3,4], Boehme *et al.*[5]). However, it is felt that the value of the scanning is not fully realized in many programs because the dose of radioactive iodine and the amount of thyrotropic hormone are kept low. Certainly there can be no doubt that the large doses of I^{131} after proper thyrotropic hormone administration (50 to 70 units), can demonstrate "functioning" other studies reported from this clinic[8] that 66% of the patients in whom metastases have been found by the heavy dose technique, have subsequently had negative scintigrams. The assumption has been made that this represents total ablation of the tissue.

This problem is a continuing one. At this time the value of the detective role of large-dose scintigrams is well

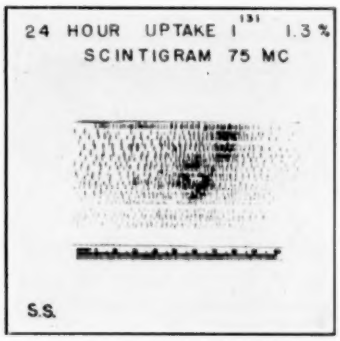

Fig. 8.—Preoperative demonstration of collection of I^{131} by metastatic tissue proved to be histologically a papillary type. S.S. Seven years after initial surgery for papillary carcinoma, appearance of several nodules in the thyroid region was noticed. Twenty-four hours after administration of 70 units of thyrotropic stimulating hormone a routine uptake of I^{131} revealed a value of 1.3% over the left nodular area. The scintigram with 75 millicuries showed intensive collection of I^{131} over the same left nodular area. At surgery a histologic diagnosis of papillary carcinoma metastatic to lymph nodes was made.

thyroid tissue that might have been missed by smaller doses (Figs. 4, 5 and 6). For this reason alone a larger dose of radioactive iodine and thyrotropic stimulating hormone seems appropriate when studying cases of thyroid cancer.

The central problem raised by administration of this sort, is whether or not any therapeutic purpose is served. Thus, if a large dose of radioactive iodine does show an area of functioning tissue which was missed by conventional techniques, can this tissue be ablated? If the amount of radiation is less than ½% of the dose given, can it be assumed that I^{131} therapy is of no value? This question is as yet, not fully answered. Evidence is at hand in established, with the therapeutic value partially so. It is hoped that continuation of this type of study can reach some answer in the next decade.

This study also shows the lack of correlation between the histologic diagnosis of the original cancer and the collection of radioactive iodine by the metastatic tissue. This can be seen in Figs. 5, 6 and 8, where positive scintigram is obtained notwithstanding the histologic diagnosis of papillary carcinoma.

Our data emphasize the lack of interference of the daily intake of thyroid U.S.P. or l-thyroxine with the stimulating effect of a proper dose

(50 to 70 units) of thyrotropic stimulating hormone (Figs. 2 to 8).

It is shown (Fig. 1) that smaller doses of TSH such as 20 units, may not be able to cause a proper stimulation of scanty residual tissue. Thus, at the present time we consider that a proper dose of thyrotropic stimulating hormone is between 50 and 70 units.

Summary. The decision to treat thyroid cancer with radioactive iodine is based on:

1) The demonstration of thyroid tissue and,

2) proof of its avidity for radioactive iodine.

The study reported here demonstrates that proper scintigram techniques after thyrotropic stimulating hormone administration can demonstrate functional tissue when conventional uptake and excretion studies are negative. Many patients would not have been treated in the presence of thyroid tissue not recognized without this procedure.

Scintigrams are made following the use of 50 to 70 units of thyrotropic stimulating hormone, with doses of 2 to 100 millicuries of radioactive iodine.

Our data also shows a lack of strict correlation between the initial histologic diagnosis and the collection of radioactive iodine by the metastases.

The significance of the findings is discussed.

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SUMMARIO IN INTERLINGUA

Le Valor Diagnostic E Therapeutic De Hormon Thyrotropic E De Scintigrammas A Forte Dosage In Le Demonstration De Metastases De Cancere Thyroide

Le decision de tractar cancere thyroide con iodo radio-active es basate super (1) le demonstration de histos thyroide e (2) le demonstration de su aviditate pro iodo radio-active.

Le studio hic reportate demonstra que le uso appropriate de technicas de scintigraphia post administrationes de stimulante hormon thyrotropic pote provar le presentia de histos functional quando le studios conventional de acceptation e excretion es negative. Numerose patientes non haberea essite tractate sin le presente technica, proque le presentia de histos thyroide in illes non esseva demonstrabile per altere methodos.

Scintigrammas es facite post le uso de 50 a 70 unitates de stimulante hormon thyrotropic, con doses de inter 2 e 100 millicuries de iodo radio-active.

Nostre datos etiam revela le absentia de un stricte correlation inter le diagnose histologic initial e le collection de iodo radio-active per le metastases.

Le signification del presente observationes es discutite.

THE REVERSAL OF CARDIOTOXIC EFFECTS OF QUINIDINE BY MOLAR SODIUM LACTATE: AN EXPERIMENTAL STUDY*

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Recently we had the opportunity to study a patient with quinidine toxicity complicated by slight hyperpotassemia whose electrocardiogram showed marked widening of the QRS complex. Administration of molar sodium lactate resulted in a return of the QRS complexes to a normal width and a concomitant rise in blood pressure. Because many of the electrocardiographic manifestations of hyperpotassemia and quinidine toxicity are similar, and in view of the known usefulness of molar sodium lactate in reversing the cardiotoxic effect of hyperkalemia (Bellet and Wasserman[2]), we decided to study the effects of molar sodium lactate in experimental quinidine toxicity in dogs.

Methods and Materials. Observations were made on two groups of animals: a control group of dogs (Group 1) receiving a continuous infusion of quinidine until death and another comparable group of dogs (Group 2) given quinidine in the same manner and treated with molar sodium lactate during various stages of quinidine toxicity. The following experiments were performed.

GROUP 1: CONTROL DOGS. Seven dogs weighing between 10 and 20 kg., were anesthetized with Pentobarbital (30 mg. per kilo) and artificial respiration instituted. A solution of quinidine gluconate in 5% glucose (6 mg. per ml.) was given at a rate of 1 mg. per kg. per min. by constant intravenous infusion. During the infusion, frequent samples of arterial blood were taken for determination of quinidine levels and plasma electrolytes; continuous electrocardiograms (Lead II), and blood pressure recordings were obtained during the entire experiment (Figs. 1 to 5). Direct blood pressure records were obtained by cannulation of the femoral artery and the use of a Sanborn twin-beam Viso-cardiette was utilized for the simultaneous recording of the blood pressure and the electrocardiogram.

GROUP 2: DOGS TREATED WITH MOLAR SODIUM LACTATE. Twelve dogs were prepared and studied in a manner identical to that of the control group. The infusion of quinidine gluconate was continued during the entire

*This work was aided by a grant from the United States Public Health Service, Grant H 141 (C7), the Heart Association of Southeastern Pennsylvania, and the Eli Lilly Company of Indianapolis, Indiana.

length of the experiment as in the control group until the animal died. Continuous quinidine infusion was maintained since its temporary cessation leads to significant changes in the cardiotoxic quinidine effects and to considerable difficulty in determining the effect of therapy. The only difference between Groups 1 and 2 was the administration of molar sodium lactate at various stages of quinidine toxicity in the latter group.

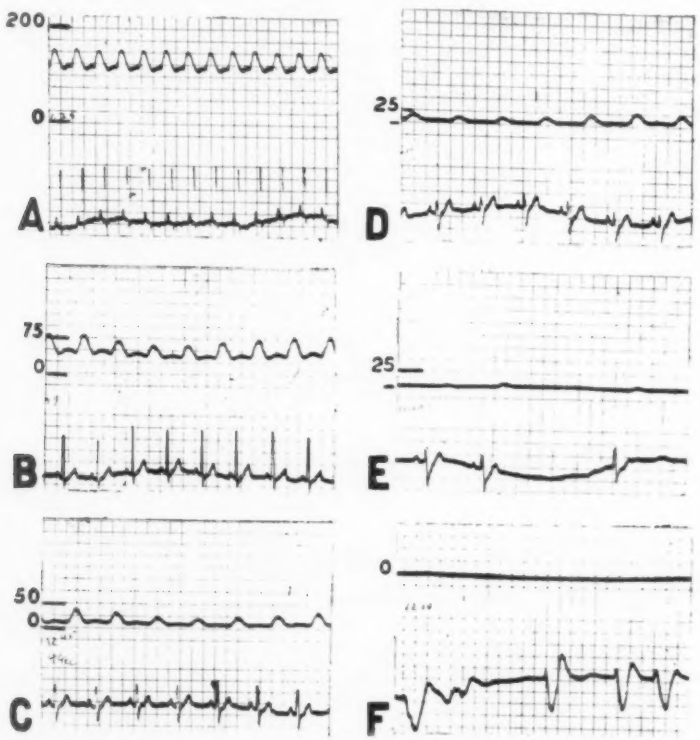

Fig. 1.—(Control). Effect of quinidine infusion on the electrocardiogram (Lead II) and blood pressure in the normal dog.

A. Control. The rate is 210 per min.; the QRS width is 0.04 sec. and the blood pressure is 155/120. The plasma potassium is 3.5 mEq./L., sodium 151.8 mEq./L.

B. Forty minutes after continuous infusion of quinidine gluconate (1 mg. per kilo per mm.) the heart rate has slowed to 120 per min.; the previously inverted T wave has become positive; the blood pressure has decreased to 70/25. The plasma quinidine level is 8.96 mg. per L., potassium 3.0 mEq./L. and sodium 145 mEq. per L.

C. Eighty-five minutes after continuous infusion of quinidine gluconate (1 mg. per kilo per mm.). The PR has increased to 0.16 sec., the QRS complex has increased to 0.08 sec., and the U wave is more prominent. The blood pressure has decreased to 40/15. The plasma quinidine level is 12.84 mg. per L., potassium 2.18 mEq. per L. and sodium 149.0 mEq. per L.

D. Two hours and 30 minutes after infusion of quinidine gluconate (1 mg. per kilo per mm.) was started. The heart rate has decreased to 80 per minute, the PR increased to 0.20 sec. and the QRS is 0.09 sec.; the blood pressure is now 25/0. The quinidine level was 29.76 mg. per L., potassium is 2.09 mEq. per L. and sodium is 141.7 mEq. per L.

E. After 3 hours of continuous quinidine infusion. The electrocardiogram shows sinus arrest with nodal escape beats. The PR interval is 0.20 sec. but the QRS complex has widened to 0.16 sec. There was no recordable blood pressure. The quinidine level was 29 mg./L., plasma potassium was 2.14 mEq. per L. and sodium was 138 mEq. per L.

F. Ten minutes after *E*. Note slow idioventricular rhythm with marked QRS widening.

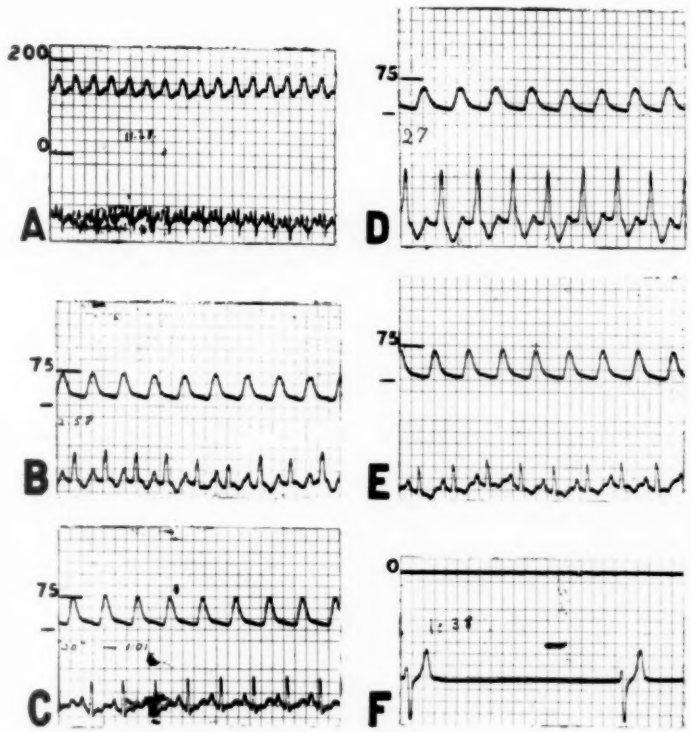

Fig. 2.—Effect of molar sodium lactate on the electrocardiogram and blood pressure during constant quinidine infusion.

A. Control electrocardiogram (Lead II). The heart rate is 210 per min., the width of the QRS is 0.04 sec., the PR interval is 0.10 sec., the blood pressure is 160/125. The plasma potassium is 3.97 mEq. per L. and sodium is 152 mEq. per L.

B. One hour and 30 minutes after continuous infusion of quinidine gluconate, note the heart rate has decreased to 110 per min., the PR interval has increased to 0.24 sec., the QRS width has increased to 0.10 sec. and the blood pressure has decreased to 65/20. The quinidine level is 14.48 mg. per L., the plasma potassium is 2.30 mEq. per L. and sodium 152.0 mEq. per L.

C. Three minutes after *B*, after 60 mEq. of molar sodium lactate has been infused. The heart rate is 110 per min., the PR interval has decreased to 0.16 sec., the QRS has narrowed to 0.07 sec. and the blood pressure is 75/15. The quinidine level has decreased to 10.48 mg. per L. The plasma potassium is 2.2 mEq. per L. and sodium is 162.0 mEq./L.

D. Twenty-three minutes after *C* (one hour and 56 minutes after the beginning of the quinidine infusion). The ventricular rate is 100 per min., there is difficulty in identifying the PR interval, the QRS is 0.14 sec., the blood pressure is 60/10. The quinidine level is 16.56 mg./L., the plasma potassium is 1.99 mEq./L. and the sodium is 156.9 mEq. per L.

E. Three minutes after *D*, 60 mEq. of molar sodium lactate has been infused. Note the P wave and PR interval have become clearly defined, the PR is 0.16 sec.; the width of the ventricular complex has decreased also to 0.08 sec. The blood pressure is 70/10, the quinidine level has decreased to 14.48 mg. per L., the plasma potassium is 1.96 mEq. per L. and sodium 172.0 mEq. per L.

F. After 2 hours and 10 minutes of continuous quinidine infusion (10 min. after *E*) note the slow ventricular rate, the width of the QRS is 0.12 sec. and there is no recordable blood pressure.

In some of the animals, molar sodium lactate was administered in two or three successive trials at various stages of quinidine toxicity. The total dose administered in each of 2 or 3 trials during a period of 3 to 5 minutes was 4 mEq. per kg. The interval between doses ranged from 20 to 30 minutes; the second and third infusion of molar sodium lactate was administered on the return of significant electrocardiographic signs of quinidine toxicity. The effects of molar sodium lactate administration were noted upon the electrocardiogram, blood pressure, and plasma quinidine and electrolyte levels. The effect of

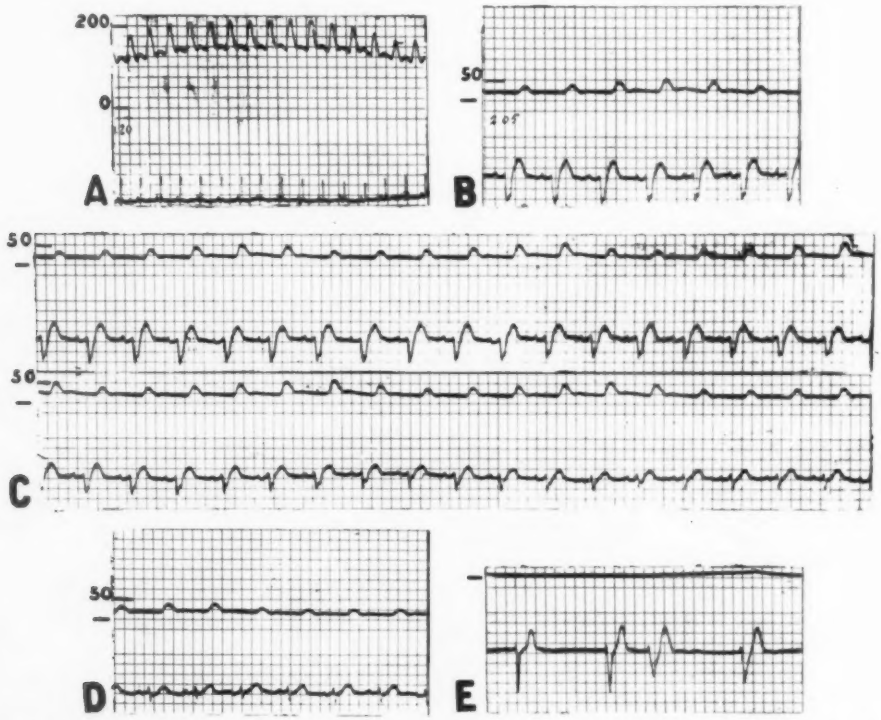

Fig. 3.—Effect of molar sodium lactate on the electrocardiogram and blood pressure during continuous quinidine infusion.

A. Control ECG (Lead II). The ventricular rate is 150 per min., QRS width is 0.04 sec., and the blood pressure is 180/115. The plasma potassium is 3.94 mEq. per L. and sodium is 143.8 mEq. per L.

B. Two hours and 45 minutes after continuous quinidine gluconate infusion. The heart rate has slowed to 64 per min., the PR interval has increased to 0.22 sec., the QRS complex has widened to 0.16 sec. and the blood pressure has dropped to 35/20. The quinidine level is 34.40 mg. per L., plasma potassium is 2.87 mEq. per L. and sodium is 133.2 mEq. per L.

C. Two hours and 53 minutes after a constant quinidine infusion. Continuous recording of the electrocardiogram and the blood pressure during the infusion of 45 mEq. of molar sodium lactate. Note the marked narrowing of the ventricular complexes from 0.18 sec. to 0.10 sec. There is no change in blood pressure. The quinidine level immediately before the infusion of molar sodium lactate was 40.80 mg. per L., the plasma potassium 3.23 mEq. per L. and sodium 131.8 mEq. per L.

D. Four minutes after *C*. One minute after the infusion of molar sodium lactate has been stopped. The ventricular rate is 64 per min., the blood pressure is 35/20, the width of the QRS complex is 0.10 sec. The quinidine level has decreased to 24.88 mg. per L. The plasma potassium is 3.11 mEq. per L. and sodium 163 mEq. per L.

E. Twenty-three minutes after *D*. Note the presence of a slow and somewhat irregular idioventricular rhythm. There is no recordable blood pressure.

norepinephrine administered in a single dose of 2 μg. per kg. was determined during the hypotensive state before and after the administration of molar sodium lactate.

Results. CONTROL GROUP. The results are shown in Figs. 1 and 6 and in Table 1. The following relatively consistent findings were obtained.

Electrocardiogram and Plasma Quinidine Levels. The electrocardiogram showed a steady progression of the well known quinidine effects; namely, slow-

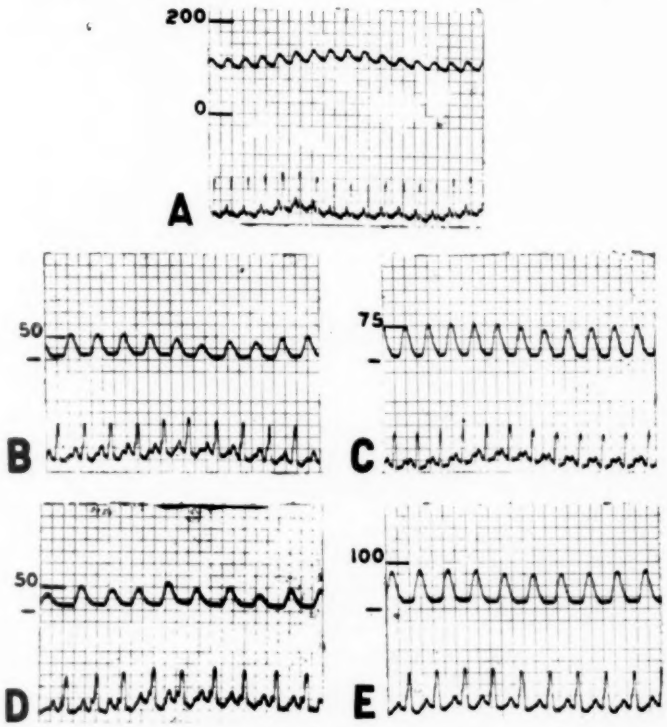

Fig. 4.—Effect of molar sodium lactate on the electrocardiogram and blood pressure during continuous quinidine infusion.

A. Control Lead II and blood pressure. There is a regular sinus rhythm and the blood pressure is 125/105 mm. Hg.

B. One hour and 32 minutes after quinidine infusion had started note the blood pressure has decreased to 50/10, and there is an increase of the PR interval with widening of the QRS complexes to 0.12 sec. The plasma quinidine level was 20 mg. per L., potassium 3.7 mEq. per L., and sodium 134 mEq. per L. At this time 50 mEq. of molar sodium lactate was given over a 3-minute period.

C. Three minutes after *B*. Following the infusion of molar sodium lactate, note the increase in the blood pressure to 75/10 and the marked narrowing of the QRS complexes from 0.12 to 0.08 sec. The quinidine level has dropped to 14.32 mg. per L., potassium 3.4 mEq. per L., sodium 150 mEq. per L.

D. Thirty minutes later, after *C*, the blood pressure has again dropped to 40/10 and there is marked widening of the QRS complexes due to continuance of the constant quinidine infusion. The quinidine level is 25 mg./L., plasma potassium 3.0 mEq. per L. and sodium 148 mEq. per L. Molar sodium lactate was again infused at this time.

E. Three minutes after *D*, note the increase in blood pressure to 80/20 mm. Hg and a marked narrowing of the QRS complexes from 0.16 to 0.12 sec. The quinidine level has decreased to 17.40 mg. per L., potassium 2.8 mEq. per L. and sodium 163 mEq. per L.

ing of the heart rate, prolongation of the PR interval, changes in the ST and T waves, lengthening of the QT interval with the appearance of a prominent U wave. These alterations occurred with quinidine concentration levels between 5 to 15 mg. per L.

Further slowing of the heart rate with increasing widening of the QRS complexes and further increase in the PR interval with decrease in the frequency of auricular beats were noted with quinidine concentrations between 15 to 25 mg. per L. Marked widening of the QRS from 0.08 to 0.12 second or more with the development of an idioventricular rhythm eventuating in ventricular standstill occurred at quinidine concentrations which ranged from 25 to 40 mg. per L. The stages of quinidine effect often were not distinct entities, but merged from one into the other. Moreover, there was considerable variation in the quinidine effects at similar plasma levels in different animals. Deviation from this usual course of events consisted in (a) the sudden appearance of QRS widening after only slight T wave changes, (b) the maintenance of P waves even with marked degrees of QRS widening, (c) occasionally, the terminal mechanism was that of ventricular fibrillation. Aside from the T and ST segment changes, the electrocardiographic changes simulate closely those observed with potassium toxicity.

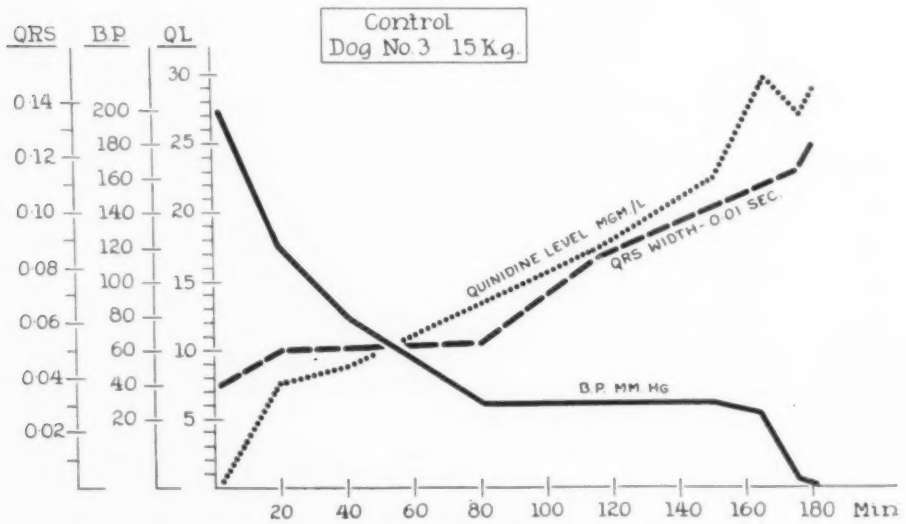

Fig. 5.—The effects of quinidine gluconate infusion upon the quinidine levels, width of the QRS complexes and blood pressure.

The ordinates indicate the width of the QRS complexes, the blood pressure and plasma quinidine levels, respectively. The abscissae represent the time periods in minutes, during which quinidine was administered. Note the gradual increase in plasma quinidine levels as the quinidine is infused. As the plasma quinidine level is increased, there is a progressive widening of the QRS complex which almost parallels the quinidine level. Not the decrease in the blood pressure level which finally drops to zero after 180 minutes of infusion with a QRS width of 0.14 second and a plasma quinidine level of 29 mg. per L.

Blood Pressure. In a general way, the blood pressure decreased progressively with increasing severity of the

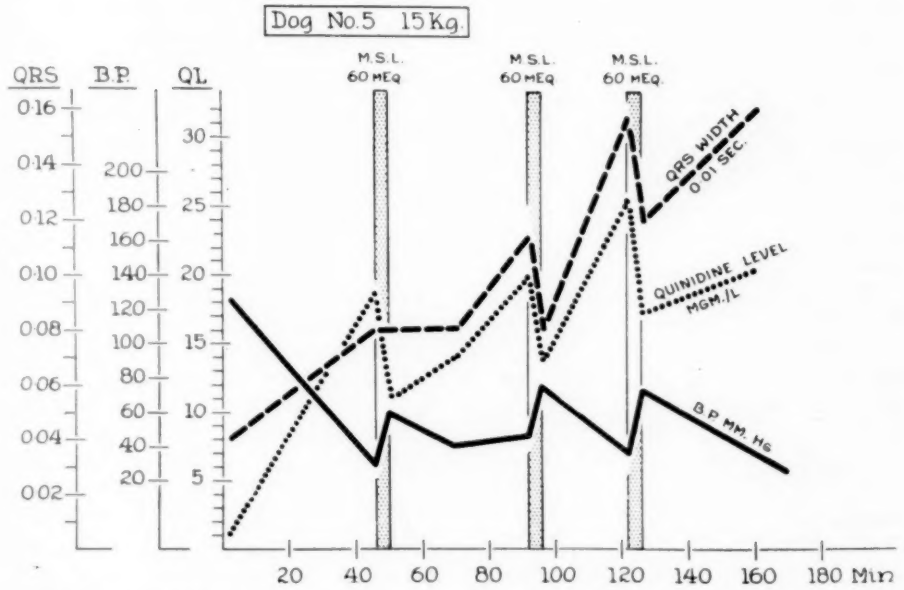

Fig. 6.—Effect of infusion of molar sodium lactate upon plasma quinidine levels, blood pressure and width of the QRS complex during quinidine toxicity.

The ordinates and abscissae are similar to those in Fig. 5. Quinidine gluconate was infused continuously as mentioned in the text. During the first 45 minutes of quinidine gluconate infusion, note the characteristic effects; namely, the increase in quinidine level, increase in QRS width and fall in blood pressure. At the 45 minute period 60 mEq. of molar sodium lactate was infused (dotted block). Note the drop in quinidine level and the increase in blood pressure. The QRS width was not materially affected at this time. With the continuance of the quinidine infusion, note the increase in plasma quinidine concentration, the increase in QRS width and the fall in blood pressure. Following the infusion of molar sodium lactate during a 5-minute period, note the drop in plasma quinidine concentration, the decrease in QRS width and the increase in blood pressure. A similar sequence of events was repeated up to the 120-minute period. Finally, the animal died after 170 minutes of continuous quinidine infusion.

TABLE 1.—ARTERIAL PLASMA LEVELS; ELECTROLYTE CHANGES DURING QUINIDINE INFUSION

Control Dog 1 Wt. 15 Kg.

Time	*Quinidine Level mg./L.*	*Na mEq./L.*	*K mEq./L.*	*Mg mEq./L.*	*CO_2 mEq./L.*	*Ca mEq./L.*
Control	0.46	151.8	3.50	1.11	16.20	5.82
22 min.	7.60	147.9	2.76	1.04	13.50	5.32
40 min.	8.96	145.4	3.00	0.79	13.05	5.12
1.24 hrs.	12.84	149.0	2.18	0.70	11.25	5.27
2 hrs.	17.20	146.0	1.93	0.73	10.80	5.47
2.32 hrs.	22.40	142.9	2.12	0.92	7.90	5.47
2.50 hrs.	29.76	141.7	2.09	0.70	6.75	5.62
3 hrs.	27.36	137.0	2.14	0.74	4.95	5.62
3.01 hrs.	29.00	138.4	2.23	0.70	4.50	5.52

electrocardiographic changes. A significant blood pressure drop was noted with the initial appearance of QRS widening and further decrease with increasing widening of the QRS (Figs. 1 to 5). The gradual decline in blood pressure continued with further deterioration of the electrocardiogram and approached the zero level with the appearance of a slow idioventricular rhythm.

Electrolyte Alterations. The electrolyte alterations following the infusion of quinidine are as follows: (a) The plasma K+ decreased by an average of 0.92 mEq./L. (range 0 to 1.7 mEq./L.), (b) the plasma Na+ decreased by an average of 12 mEq./L. (range 0 to 15 mEq./L.), (c) the plasma CO_2 decreased by an average of 4.8 mEq./L. (range 0 to 9 mEq./L.), (d) the plasma magnesium decreased by an average of 0.44 mEq./L. (range 0 to 0.73 mEq./L.). The electrolyte alterations in a typical case are shown in Table 1. In a general way, there was a decrease in potassium, sodium, and magnesium and the development of acidosis. The pH (not shown in Table 1) decreased by an average of 0.2 unit in four experiments. The most marked changes were observed with increasing electrocardiographic abnormalities and a drop in blood pressure. It is of interest that in spite of the acidosis produced by quinidine infusion, a decrease in plasma potassium was observed. This may be due to the action of quinidine which prevents the efflux of potassium from the cells and increases the influx of potassium into the cells (Conn and Wood[8], Holland[13,14]).

GROUP 2: DOGS TREATED WITH MOLAR SODIUM LACTATE. Administration of molar sodium lactate resulted in a reversal of the electrocardiographic effects of quinidine toxicity and an increase in the blood pressure. The effects of molar sodium lactate administered in a typical case are shown in Fig. 2. This reversal is noted if the molar sodium lactate is given before or during the third stage of quinidine toxicity* (widened QRS). In the final stage (slow idioventricular rhythm) or when the blood pressure is extremely low, no reversal of these effects is noted.

The following effects were noted following molar sodium lactate infusion.

Electrocardiogram. Instead of the gradual deterioration of the electrocardiographic patterns as noted in the controls, narrowing of the QRS complexes was observed within 2 to 5 minutes following the beginning of the infusion of molar sodium lactate, and this improvement persisted for 5 to 15 minutes in spite of the continued infusion of quinidine. This improvement was more marked after the second or third infusion of molar sodium lactate.

Effect on the Blood Pressure. The blood pressure was usually increased above the low level observed during quinidine toxicity. The rise in blood pressure was parallel to the electrocardiographic improvement. Sometimes, even with salutary electrocardiographic improvement, the elevation of the blood pressure was slight. When the control blood pressure level during quinidine infusion dropped to about 40 mm. Hg, improvement was less likely to occur, although this did occasionally happen.

Effect of Norepinephrine. The effect of norepinephrine was studied in 4 animals prepared in an identical manner as those treated with molar sodium lac-

*The stages of quinidine toxicity may be divided as follows: Stage 1 consisted of T wave, ST segment, and U wave alterations; stage 2, a decrease in auricular activity with slight QRS widening; stage 3, conspicuous QRS widening and A-V dissociation; stage 4, slow idioventricular rhythm.

tate. Norepinephrine was infused in a single dosage of 2 mcg. per kg. during the state of hypotension produced by quinidine. An increase in blood pressure with an average of 30 mm. resulted when the infusion was instituted in the early and moderately advanced stage of toxicity. When used after molar sodium lactate, an additional increase in blood pressure (10 to 20 mm.) was observed but ectopic rhythms occasionally appeared. When used in the advanced stages, no vasopressor effect was observed. The effect on QRS widening itself was slight; this was less than that which occurred after molar sodium lactate.

electrocardiographic and blood pressure changes to be reached as were present immediately before the administration of molar sodium lactate. Occasionally, the periods of improvement were shorter.

Electrolyte Alterations After the Infusion of Molar Sodium Lactate (The typical changes following infusion of molar sodium lactate are shown in Table 2).

(a) The plasma potassium value decrease in the control experiments following quinidine infusion averaged 0.92 mEq. per L. This level was further decreased by molar sodium lactate infusion by an average of 0.4 mEq. per

TABLE 2.—ARTERIAL PLASMA LEVELS; ELECTROLYTE CHANGES AFTER MOLAR SODIUM LACTATE IN DOGS WITH CONSTANT QUINIDINE INFUSION

Dog 15

Time	*Quinidine Level mg./L.*	*Na mEq./L.*	*K mEq./L.*	*Mg mEq./L.*	*CO_2 mEq./L.*	*Ca mEq./L.*
0 time	Cont. 0.10	152.8	3.97	1.71	16.20	5.57
50 min.	MSL 16.80	143.0	3.19	1.08	13.05	4.68
53 min.	11.40	156.5	2.86	1.18	16.65	3.98
1.14 hrs.	12.60	152.6	2.35	1.08	16.20	4.58
1.30 hrs.	MSL 14.48	150.0	2.30	0.87	18.00	4.38
1.33 hrs.	10.40	162.0	2.20	1.03	20.25	3.98
1.56 hrs.	MSL 16.56	156.9	1.99	1.15	22.05	4.28
2.04 hrs.	14.48	172.0	1.96	1.08	21.60	3.98

Quinidine Levels. In the control animals, the quinidine level gradually and progressively increased with continuation of the infusion and accompanying increase in the degree of quinidine toxicity. Following molar sodium lactate infusion, there was a consistent decrease in quinidine concentration which ranged from 3.2 to 7.6 mg. per L. which appeared within about 3 to 5 minutes (Table 1). This drop in quinidine level was accompanied by improvement in the electrocardiogram and increase in blood pressure. Following the molar sodium lactate infusion, it required the continuous infusion of quinidine for a period of 20 to 30 minutes for the same plasma levels and the

L., making a total average decrease of 1.32 mEq. per L., (b) the plasma sodium increased by an average of 25 mEq. per L. (range 7 to 80 mEq. per L.), (c) the plasma CO_2 increased by an average of 3.19 mEq. per L. (range 0 to 5.85 mEq./L., (d) the serum magnesium showed no significant changes from that due to quinidine alone, (e) the calcium decreased by an average of 0.74 mEq./L. (range 0.25 to 1.24 mEq. per L.). The effect on the electrolyte pattern in a typical case is shown in Table 2. In a general way, the infusion of molar sodium lactate resulted in an increase in serum sodium and CO_2 combining power with a decrease in potassium; there was a

diminution in the degree of acidosis and a tendency to produce an alkalosis. These effects are essentially opposite to those of quinidine alone.

Discussion. MECHANISM OF QUINIDINE EFFECTS. Prior to a discussion of the beneficial effects of molar sodium lactate on quinidine toxicity, it might be well to review the mechanisms involved in the production of quinidine effects. Quinidine manifests the following effects on the heart: it tends to paralyze the vagus, it increases the refractory period by a direct effect on the muscle and it slows conduction, the transmission intervals increasing to as much as twice the normal. The clinical results are due chiefly to the effects of quinidine on the refractory period and on conduction (Bellet[1], Lewis[17]). Toxic effects may occasionally be observed following therapeutic doses in sensitive individuals. In a patient with a normal intraventricular conduction time, an increase of 50% in QRS width is dangerous and it probably should not be increased above 25% (Hyman[15], Lewis[17], Sokolow[19]). An extra hazard apparently exists in the presence of an already prolonged intraventricular conduction time, since further widening may help to induce serious ectopic rhythms, particularly ventricular fibrillation. The practice of withholding quinidine after the QRS is prolonged 25 to 50% or above 0.12 to 0.14 of a second appears to be desirable (Hyman[15], Sokolow[19]).

In the human subject quinidine produces a protein anabolic effect (Furman and Howard[11]) and pronounced changes in carbohydrate metabolism (Uyeki, Geiling and Dubois[20]). This is manifested by inhibition of glucose utilization as shown by an impaired glucose tolerance curve. In myocardial slices and tissue homogenates, quinidine was found to (a) depress oxygen uptake (Webb, Saunders and Nakamura[21]), (b) inhibit anaerobic glycolysis, (c) impair the oxidation of glucose pyruvate, citrate, fumarate, malate and oxaloacetate, possibly by interfering with transphosphorylating enzymes (Uyeki, Geiling and Dubois[20], Webb, Saunders and Nakamura[21]), (d) decrease adenosine triphosphatase activity inhibiting phosphate bond utilization (Webb, Saunders and Nakamura[21]). It has been suggested that depression of oxidative metabolism may be partially responsible for the pharmacological effect of quinidine (Webb, Saunders and Nakamura[21]).

Quinidine also exerts a powerful effect upon ion exchange across the cell membrane, resulting in an increase in myocardial K+ and decreased myocardial Na+ concentration (Conn and Wood[8], Holland[13,14], Karki, Burn and Burn[16]). That these changes are of significance is demonstrated by the fact that by lowering extracellular K+ and thereby interfering with the effects of quinidine on ionic flux (Holland[13]), the quinidine effect could be inhibited. Holland suggests that these changes are, in turn, secondary to changes in acetylcholine turnover[13].

The hypotensive effects of quinidine are apparently due to the direct depression of the heart muscle and peripheral vasodilatation (Ferrer *et al.*[10]).

The reversal of the cardiotoxic effects of quinidine by molar sodium lactate is of considerable interest. These changes resemble, in a general way, the reversal of cardiotoxic potassium effects by a similar infusion.

MECHANISM OF MOLAR SODIUM LACTATE EFFECTS. The mechanisms of molar sodium lactate effects may be described under four headings: (a) decrease in plasma quinidine concentrations, (b) decrease in potassium level and a shift of the pH to the alkalotic side, (c) effect of the lactate and (d) increase in blood pressure with

resultant improvement in renal function and tissue blood flow.

(a) *Decrease in quinidine concentration.* A decrease in quinidine concentration occurs quite rapidly and is probably the result of the expansion of the extracellular space. This would result in a smaller concentration available for a depressing effect on cardiac tissue and the production of peripheral vasodilatation.

(b) *Decrease in serum potassium.* A significant decrease of serum potassium occurs rather rapidly following injection of molar sodium lactate. This is due to a combination of various factors: 1) expansion of the extracellular space, 2) intracellular shift of potassium, 3) increase in serum sodium which tends to decrease the potassium effect, 4) increase in urinary excretion of potassium (Singer *et al.*[18]). A marked increase in rhythmicity of cardiac pacemakers and an increase in conduction have been observed to occur in both man and animals (Bellet, Wasserman and Brody[3,4]), in the presence of alkalosis and decreased serum potassium.

With the development of quinidine toxicity, that is, when the QRS complexes were widened and a hypotension was present, the CO_2 combining power and pH dropped significantly. This state tends to further increase the circulatory impairment. Molar sodium lactate, by decreasing the amount of acidosis and shifting the pH to the alkalotic side, tends to lower the plasma potassium further, increasing the rhythmicity of the cardiac pacemakers and tending to improve conduction (Hoffman and Suckling[12]).

Finally, there is some evidence which suggests that quinidine and potassium manifest synergistic effects on the heart; an increased serum potassium increases the quinidine effect, while a lower serum potassium tends to decrease it (Holland[13,14]). Thereafter, a simultaneous decrease in quinidine and potassium concentration in the plasma would decrease cardiotoxicity.

(c) *Effect of the lactate.* There is evidence that the heart muscle can utilize lactate for direct provision of energy (Bing *et al.*[5], Clark, Gadder and Stewart[7], Evans[9]). The lactate may act directly as added substrate to the Krebs cycle and may be converted to pyruvate via the coenzyme diphosphopyridine nucleotide, circumventing the intermediate steps of conversion of glucose to pyruvate. This may, in effect, serve to act directly in the oxidative metabolic mill of the Krebs cycle and to utilize more efficiently and conserve the energy of the cell.

(d) *Increase in blood pressure.* The increase in blood pressure observed following infusion of molar sodium lactate during quinidine toxicity may be due to various factors: 1) diminution of the depressant effects of quinidine with a resultant increase in myocardial contractility, 2) increase in cardiac output and coronary artery blood flow, 3) osmotic effect by suddenly increasing the blood volume, and 4) a combination of the above effects. The increase in blood pressure is associated with an increased cardiac output, increased renal and general tissue blood flow.

Summary. Because of the similarity of the cardiotoxic effects of quinidine to those of hyperpotassemia and the beneficial effects of molar sodium lactate in reversing the cardiotoxicity of potassium, the effect of molar sodium lactate was studied in the dog.

Two series of dogs were studied. In one, the control group, quinidine gluconate was given by continuous infusion until the animal died. In the second group, molar sodium lactate

was administered at various stages of quinidine toxicity.

The cardiotoxic effect of quinidine as manifested by the electrocardiographic alterations and hypotension was reversed by the use of molar sodium lactate. This reversal could be observed repeatedly. However, in the far advanced stages of cardiotoxicity where a slow idioventricular rhythm was present and the blood pressure was close to zero, molar sodium lactate was of less efficacy or was entirely ineffective.

It is suggested that beneficial effects of molar sodium lactate are due to the following factors: (a) decrease in plasma quinidine concentration, (b) decrease in serum potassium with the shift of the pH to the alkalotic side, and (c) the effect of the lactate which might be used directly for energy production.

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(Interlingua on page 189)

A REVERSAL OF THE CARDIOTOXIC EFFECTS OF PROCAINE AMIDE BY MOLAR SODIUM LACTATE*

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Previous work from our laboratory demonstrated the beneficial effect of molar sodium lactate in the therapy of quinidine toxicity. Since quinidine and procaine amide have similar pharmacological effects we considered it of interest to also study the action of molar sodium lactate in experimental procaine amide toxicity in the dog.

Methods and Materials. A control group (Group 1) received a continuous infusion of procaine amide until death of the animal. The second group, prepared in identical manner, was given molar sodium lactate during various stages of procaine amide toxicity†. The following experiments are described in detail.

GROUP 1: CONTROL DOGS TREATED WITH PROCAINE AMIDE. Five dogs weighing between 10 and 20 kg. were anesthetized and prepared in a manner similar to that described in our studies on quinidine toxicity (Bellet *et al.*[1]). A solution of procaine amide hydrochloride in 5% glucose was infused at the rate of 40 mg. per min. until the death of the animal. During the infusion, frequent samples of arterial blood were taken to determine the plasma procaine amide level, pH and plasma electrolytes. Continuous electrocardiograms (Lead II) and blood pressure recordings were obtained during the entire experiment (Fig. 1).

GROUP 2: DOGS TREATED WITH PROCAINE AMIDE AND MOLAR SODIUM LACTATE. Ten dogs were prepared and studied in a manner similar to the control group. The infusion of procaine amide was continued during the entire length of the experiment as in the control group until the animal died, since its temporary interruption led to marked and unpredictable changes in the cardiotoxic effects. By this method we were able to compare the results of therapy obtained in this group (McClendon, Hansen and Kinsman[5]) with the control group.

When the toxic effects of procaine amide became evident, these dogs were given 4 mEq. per kg. of molar sodium lactate over a

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†The degree of procaine amide effect on the electrocardiogram (stages 1 to 4) are similar to those described with quinidine toxicity[1].

period of time which ranged between 3 to 5 minutes. In some of the animals, molar sodium lactate was administered in 3 to 4 successive trials at various stages. The usual interval between doses was 15 to 20 minutes. The second, third and fourth infusions of molar sodium lactate were administered upon the return of significant electrocardiographic abnormalities (usually widening of the QRS complex or runs of ventricular flutter-fibrillation).

The effects of procaine amide infusion (in the first group) and the effects of molar sodium lactate (in the second group) during the infusion of procaine amide in dogs were noted upon the electrocardiogram, blood pressure, arterial plasma levels of procaine amide, pH and serum electrolytes.

Results. CONTROL GROUP. In this group the following effects were noted on the electrocardiogram, blood pres-

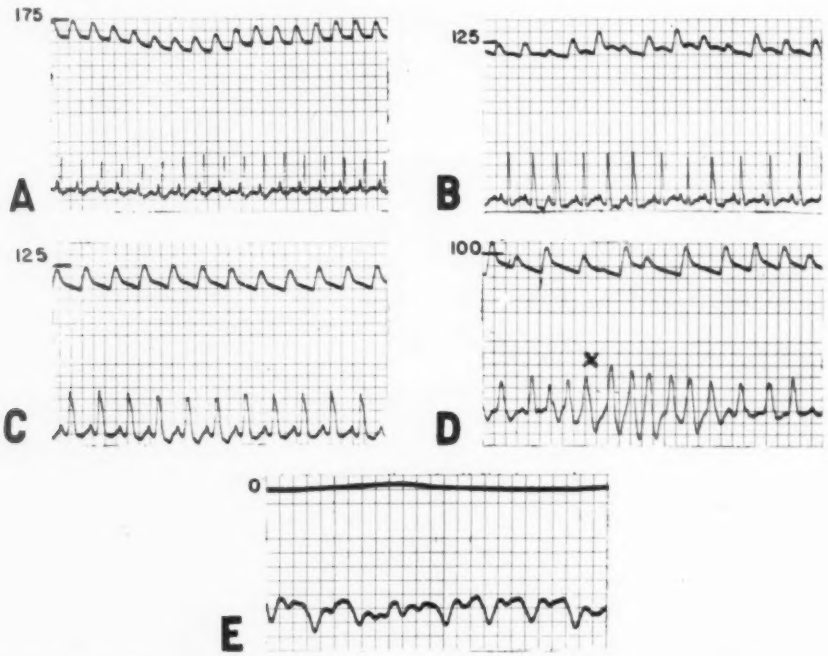

Fig. 1.—Blood pressure and electrocardiogram in the dog during procaine amide toxicity.

A. Control tracing in Lead II. The blood pressure is 180/125. Continuous procaine amide infusion was started at a rate of 40 mg. per min. Plasma potassium 4.27 mEq. per L. and sodium 142.3 mEq. per L.

B. Thirty-five minutes after. There is a decrease in blood pressure to 135/100 and a decrease in the rate from 166 to 140 per minute; the QRS complexes are widened and the T waves inverted. The plasma procaine amide is 13.5 mg. per L., potassium 3.72 mEq. per L. and sodium 142.3 mEq. per L.

C. Thirty minutes after *B*. The blood pressure is 125/75, there is marked widening of the ventricular complexes (0.16 sec.) and the PR interval is slightly prolonged. The plasma procaine level 22.8 mg. per L., potassium 3.43 mEq. per L., and sodium 140.0 mEq. per L.

D. After one hour and forty-five minutes of continuous procaine amide infusion (40 minutes after *C*), note that in spite of the widening of the ventricular complexes (0.16 sec.) and runs of tachycardia and ventricular flutter at X, the blood pressure is fairly well maintained (100/50). The plasma procaine amide level 33.4 mg. per L., potassium 3.27, and sodium 133.3 mEq. per L.

E. Note the development of ventricular fibrillation as the terminal mechanism after 1 hour and 45 minutes of continuous procaine amide infusion.

sure and electrolytes (Fig. 1 and Table 1).

Effect of Procaine Amide on the Electrocardiogram. With a continuous infusion of procaine amide, there is a gradual slowing of the heart rate, slight increase in the PR interval and ST–T wave changes at plasma procaine amide concentrations between 5 to 15 mg. per L.

Progression of the procaine amide effects upon the electrocardiogram with increased PR interval and widening of the QRS complexes to 0.08 to 0.10 sec. occurred at a procaine amide level of 15 to 25 mg. per L. Premature auricular beats occurring either as isolated beats or short paroxysms of tachycardia appeared frequently during this stage of toxicity.

Further widening of the QRS complexes to 0.12 sec. or more, with runs of ventricular flutter-fibrillation, were seen at a plasma procaine amide level of 25 mg. per L. or higher. Finally, after runs of ventricular flutter, the dog died either in ventricular fibrillation or with a slow idioventricular rhythm, usually at plasma procaine amide levels which ranged between 40 and 50 mg. per L. These stages of procaine amide toxicity usually manifested the same sequence (Fig. 1).

Effect on the Blood Pressure. Procaine amide administered intravenously manifests well known effects. These hypotensive effects were not as marked as those observed with quinidine during comparable stages of toxicity. It is of interest that a significant blood pressure was observed even during the presence of serious arrhythmias, for example, ventricular flutter (Fig. 1).

Effect of the Procaine Amide Infusion on the Plasma Electrolytes. After the administration of procaine amide in solution of 5% glucose, the following electrolyte changes were relatively consistently observed: The plasma potassium value decreased by an average of 0.82 mEq. per L. (range 0.4 to 1.1 mEq. per L.). The plasma sodium value decreased by an average of 15 mEq. per L. (range 14 to 20 mEq. per L.). The blood pH values decreased by an average of 0.2 of a unit (range 0.1 to 0.3 of a unit), the serum calcium level decreased by an average of 0.9 mEq. per L. (range 0.7 to 1.2 mEq. per L.). The serum chloride level decreased by an average of 7 mEq. per L. (range 3 to 10 mEq. per L.). The serum CO_2 values decreased by an average of 4.5 mEq. per L. (range 2 to 7 mEq. per L.). The serum magnesium decreased by an average of 0.4 mEq. per L. (range 0.3 to 0.4 mEq. per L.).

TABLE 1.—ELECTROLYTE CHANGES DURING PROCAINE AMIDE TOXICITY

Time	*K* *mEq./L.*	*Na* *mEq./L.*	*pH* *0.1 unit*	*Ca* *mEq./L.*	*Cl* *mEq./L.*	*CO_2* *mEq./L.*	*Mg* *mEq./L.*	*P.A.** *mg./L.*
0 time	4.27	145.8	7.42	5.82	105	15.75	1.84	0
20 min.	4.01	140.0	7.40	5.53	100.9	13.50	1.69	12.0
48 min.	3.72	142.3	7.36	5.53	100.9	12.15	1.50	13.5
1.13 min.	3.43	140.0	7.17	5.42	91.2	12.60	1.47	22.8
1.18 min.	3.31	134.7	7.15	5.22	102.0	11.70	1.45	33.4
1.25 min.	3.27	133.3	7.15	5.12	102.0	11.25	1.47	33.4
1.30 min.	3.18	131.0	7.14	4.63	95.1	12.15	1.47	54.3

*Plasma procaine amide levels

GROUP 2: DOGS TREATED WITH MOLAR SODIUM LACTATE. The administration of molar sodium lactate resulted in a reversal of the electrocardiographic ef-

fects of procaine amide toxicity, an increase in the blood pressure and a decrease in the degree of acidosis. The effects of the administration of molar sodium lactate in a typical case are shown in Fig. 2. Note the increased blood pressure and reversal of the electrocardiographic abnormalities in the various stages of toxicity. This improvement is noted even in the rather severe stages of toxicity. The terminal stage, with a slow idioventricular rhythm and an extremely low blood pressure, is irreversible.

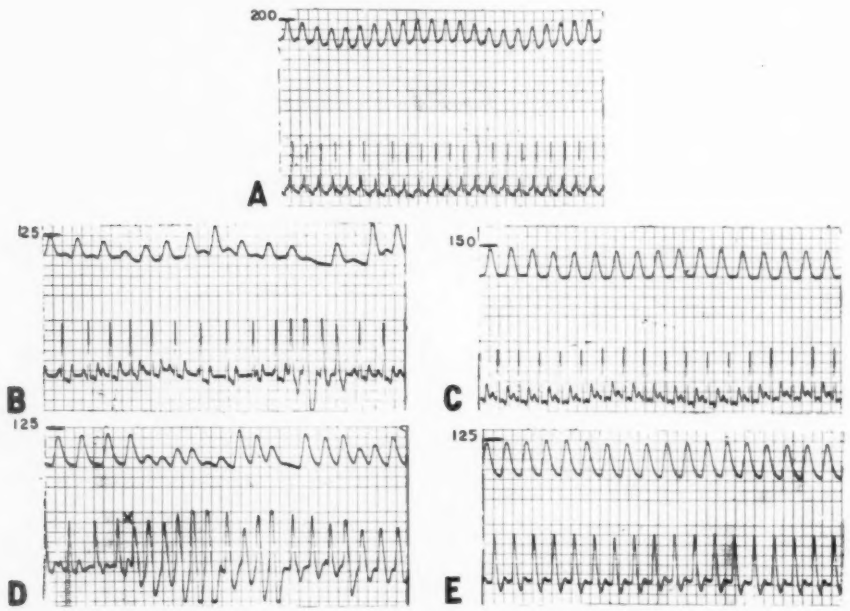

Fig. 2.—Effect of molar sodium lactate on the electrocardiogram and blood pressure during procaine amide toxicity.

A. Control. Electrocardiogram Lead II. Blood pressure is 180/130. The plasma potassium was 4.58 mEq. per L. and sodium 152 mEq. per L.

B. Twenty-two minutes after procaine amide infusion was started at 40 mg. per kg. per min. the blood pressure has fallen to 125/75. The ventricular rate has slowed, the rhythm is irregular due to aberrant beats with periods of A–V dissociation. The plasma procaine amide level was 29.7 mg. per L., potassium 4.73 mEq. per L. and sodium 152.0 mEq. per L. The infusion of molar sodium lactate was started at the end of *B*.

C. Three minutes after *B*, note the increase in blood pressure to 150/75 and the restoration of a normal sinus rhythm; the aberrant beats noted in *B* have disappeared. The plasma procaine amide level has decreased to 26.7 mg. per L., the potassium to 3.9 mEq. per L. and sodium increased to 165.7 mEq. per L.

D. Thirty minutes after *C*, note the runs of ventricular flutter at X. In spite of the marked electrocardiographic abnormality, the effect on the blood pressure is relatively slight (a drop of only 50 mm. from *C* to *D*). The plasma procaine amide level has increased to 40 mg. per L., the potassium is 3.16 mEq. per L. and sodium 161 mEq. per L. At the end of *D*, molar sodium lactate (60 mEq.) was administered.

E. Four minutes after *D*, note the increase in blood pressure to 120/30. The marked irregularity and period of ventricular flutter has been replaced by a regular rhythm. The plasma procaine amide level was 38 mg. per L., potassium 3.16 mEq. per L. and sodium 161.2 mEq. per L. Twenty minutes later, the dog died in ventricular fibrillation.

The following effects were noted following molar sodium lactate infusion:

Effect on the Electrocardiogram. Administration of molar sodium lactate produced marked improvement in the electrocardiogram even in the stage of severe toxicity, as noted by marked narrowing of the widened ventricular complexes, disappearance of aberrant and premature beats, A–V dissociation, and runs of ventricular flutter-fibrillation (Figs. 2 to 4). In one case, the administration of 10 mEq. of molar sodium lactate during an established idioventricular rhythm resulted in a return to a regular sinus rhythm (Fig. 4*b*). This improvement usually persisted for 15 to 20 minutes but it was often more transient than that observed during treatment of quinidine toxicity.

Effect on the Blood Pressure. Increase in the blood pressure levels (except in far advanced stages of toxicity) resulted from the administration of molar sodium lactate, usually within 3 to 5 minutes. Such improvement was observed even when the blood pressure level preceding the infusion of molar sodium lactate was 40 mm. or lower. Occasionally the electrocardiographic improvement was not accompanied by a notable increase in blood pressure (Fig. 4).

Plasma Procaine Amide. Instead of the gradual increase of the plasma procaine amide levels due to the continuous infusion of procaine amide as seen in the control animals, the administration of molar sodium lactate induced a consistent fall in the levels of procaine amide which ranged from 3 to 13 mg. per L. with an average of 5.5 mg. per L. This maximum decrease in the plasma concentration of procaine amide was obtained immediately after the infusion of molar sodium lactate was stopped. Usually (as observed with quinidine), it required the continuous infusion of procaine amide for a period of 15 minutes to attain plasma levels similar to those observed preceding the infusion of molar sodium lactate; occasionally these periods of improvement were shorter (5 to 10 minutes).

TABLE 2.—ELECTROLYTE CHANGES AFTER THE INFUSION OF MOLAR SODIUM LACTATE IN A DOG WITH PROCAINE AMIDE TOXICITY

Time	*K* mEq./L.	*Na* mEq./L.	*pH* 0.1 unit	*Ca* mEq./L.	*Cl* mEq./L.	CO_2 mEq./L.	*Mg* mEq./L.	*P.A.** mg./L.
0 time	4.57	144.2	7.43	4.73	104	14.4	1.77	0
50 min.	4.20	138.9	7.32	4.63	105	10.3	1.84	22.7
1.15 min.	3.93	131.3	7.21	4.56	97	8.5	1.56	33.8
1.40 min. MSL	3.62	135.0	7.20	4.43	101.2	8.1	1.87	38.8
1.43 min.	3.47	151.0	7.24	4.03	94.1	12.6	1.77	25.3
1.55 min. MSL	3.28	148.8	7.28	4.13	92.1	11.70	1.84	29.0
1.58 min.	2.89	156.5	7.31	4.01	89	11.70	1.56	24.7

*Plasma procaine amide levels

Electrolyte Alterations following the Infusion of Molar Sodium Lactate. (The typical changes following infusion of molar sodium lactate are shown in Table 2). a) The serum potassium value decreased further after infusion of molar sodium lactate by an average of 0.5 mEq. per L. making a total average decrease of 1.32 mEq. per L., b) the serum sodium increased by an average of 14 mEq. per L. (range 8 to 22 mEq. per L.), c) the serum CO_2 increased by an average of 4.3 mEq.

per L. (range 0 to 13 mEq. per L.), d) the serum magnesium showed no significant changes after the infusion of molar sodium lactate, e) the serum calcium decreased by an average of 0.92 mEq. per L. (range from 0 to 1.6 mEq. per L.), f) the pH increased by an average of 0.09 of a unit (range 0 to 0.2 unit), g) the serum chlorides decreased by an average of 9 mEq. per L. (range 6 to 20 mEq. per L.).

Quinidine and procaine amide produced essentially similar electrolyte changes, namely, decrease in serum Na, K, Ca, Cl, and Mg with production of acidosis (decreased pH and CO_2). Following the infusion of molar sodium lactate similar effects were noted

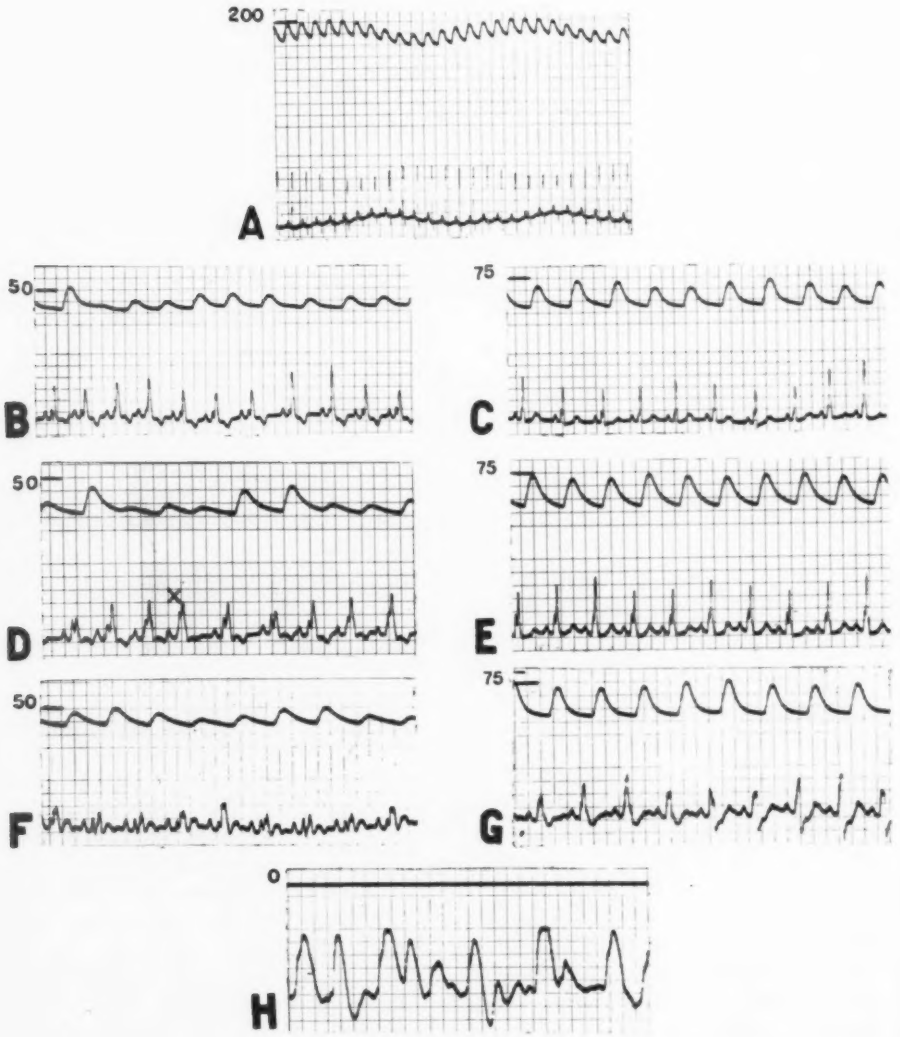

Fig. 3.—Legend on opposite page.

upon the electrolyte pattern; there was a decrease in the degree of acidosis, with increased plasma CO_2, pH, Na, and a decrease in K, Ca and Cl.

Discussion. COMPARISON OF THE CARDIOTOXIC EFFECTS OF QUINIDINE AND PROCAINE AMIDE. While the electrocardiographic and hypotensive effects of quinidine and procaine amide are qualitatively similar, there are many notable differences between these two drugs. The initial electrocardiographic effects (T waves and QT effects) are similar. However, with increased degrees of QRS widening, a depressed atrial pacemaker and A–V dissociation are more common with quinidine, while premature beats, episodes of paroxysmal tachycardia and flutter-fibrillation are more common with procaine amide toxicity.

At similar stages of QRS widening, the hypotensive effects were observed earlier and were more pronounced with quinidine. Marked hypotension was often observed in early stages of quinidine toxicity; on the other hand, with procaine amide a fairly satisfactory blood pressure was maintained even in the advanced stages of toxicity (Fig. 1). Moreover, striking improvement in the electrocardiogram and blood pressure was more consistently observed after molar sodium lactate infusion during procaine amide toxicity (Figs. 2 to 4).

However, the electrocardiographic improvement (with continuous procaine amide infusion) was usually maintained for a shorter period (3 to 10 min.) as compared with the 15- to 30-minute period of improvement during quinidine infusion.

The abolition of atrial activity with quinidine in the early stages of toxicity and its persistence with procaine

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Fig. 3.—Effect of molar sodium lactate on the electrocardiogram and blood pressure during procaine amide toxicity.

A. Control blood pressure and electrocardiogram. The plasma potassium was 4.52 and sodium 144.5 mEq. per L.

B. Forty minutes after continuous intravenous infusion of procaine amide at a rate of 40 mg. per min. The blood pressure has dropped to 40/10, the ventricular rate from 260 to 100 per minute, the QRS complexes have widened and the PR interval is prolonged. The plasma procaine amide level was 19.7 mg. per L., potassium 4.48 mEq. per L. and sodium 138.0 mEq. per L. At the end of *B*, 50 mEq. of molar sodium lactate was started.

C. Four minutes after *B*. The blood pressure has increased to 60/15, the width of the QRS complexes decreased from 0.12 to 0.08 of a second. The procaine amide level has decreased to 15.3 mg. per L., potassium 3.13 mEq. per L. and sodium 151.4 mEq. per L.

D. Twenty minutes after *C*, note the average blood pressure is 30/10. The width of the QRS complex has increased to 0.16 of a second, and occasional premature atrial beats are present at X. The plasma procaine amide level was 23.8 mg. per L., potassium 3.02 mEq. per L. and sodium 147.0 mEq. per L. Molar sodium lactate infusion was started at the end of *D*.

E. Five minutes after *D*. Note that the blood pressure increased to 60/10 and the abolition of premature beats, the width of the QRS complex has decreased from 0.16 to 0.10 of a second. The plasma procaine amide level has decreased to 17.4 mg. per L., potassium is 2.47 mEq. per L. and sodium 153.8 mEq. per L.

F. Fifteen minutes after *E*. The blood pressure had dropped to 40/15 and the width of the QRS has become markedly increased to 0.20 of a second. The plasma procaine amide level was 25.8 mg. per L., potassium 2.41 mEq. per L. and sodium 146.5 mEq. per L.

G. Four minutes after *F*. After the infusion of 50 mEq. of molar sodium lactate, note there is an increase in the blood pressure to 75/15 and the width of the QRS complex has decreased from 0.20 to 0.12 of a second. Plasma procaine amide level was 20 mg. per L., potassium 1.84 mEq. per L. and sodium 171.2 mEq. per L.

H. Thirty-five minutes after *G*. The dog died in ventricular fibrillation at a plasma procaine amide concentration of 46 mg. per L.

amide even with advanced toxicity suggests that quinidine manifests a more powerful effect than procaine amide on the atrium.

The reversal of the electrocardiographic effects can be obtained even in the far advanced stages of procaine amide toxicity, while the presence of A–V dissociation during quinidine toxicity is usually a sign of an irreversible stage of toxicity.

The above findings suggest that the cardiac depressant effects of procaine amide are less marked and that the possibility of reversal of the cardiotoxic effects is somewhat better with procaine amide, than with quinidine.

THE MECHANISM OF PROCAINE AMIDE EFFECTS. The effects of procaine amide are quite similar to those of quinidine although they have not been studied as extensively as the latter drug. Pro-

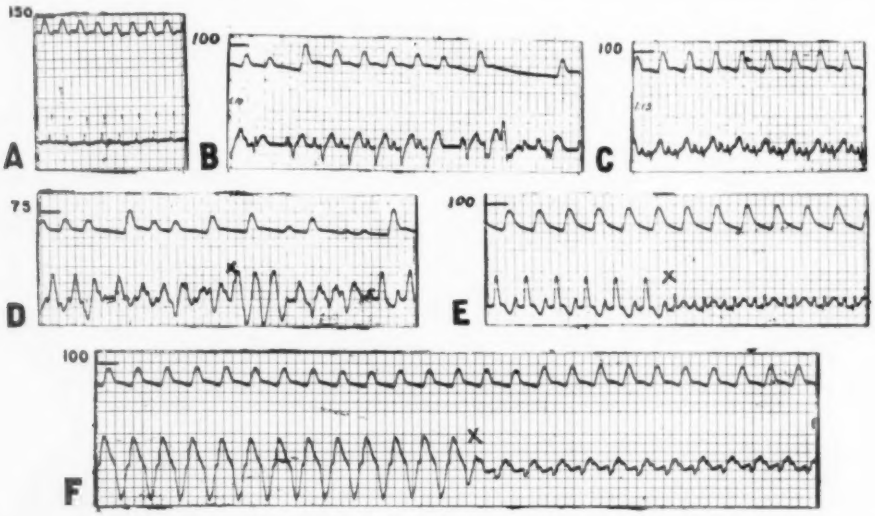

Fig. 4*a* and 4*b*.—Effect of molar sodium lactate on the electrocardiogram and blood pressure during procaine amide toxicity.

A. Control tracing. The blood pressure is 140/100, electrocardiogram (Lead II). The plasma potassium is 4.57 and sodium is 142 mEq. per L.

B. After one hour and 30 minutes of procaine amide infusion, note the drop in blood pressure to 80/50 and the appearance of marked widening of the QRS with multiple ectopic and aberrant beats. The plasma procaine amide level is 38.8 mg. per L., potassium 3.62 mEq. per L. and sodium is 135 mEq. per L. At the end of strip *B*, 60 mEq. of molar sodium lactate was administered.

C. Three minutes after *B*, note the increase in blood pressure to 100/50. There is now a normal sinus mechanism and the QRS width has narrowed. The plasma procaine amide level decreased to 25 mg. per L., the plasma potassium is 3.47 and sodium is 151.0 mEq. per L.

D. Ten minutes after *C*, the blood pressure has decreased to 50/25 due to the continuous infusion of procaine amide. Note that there is marked widening of the normally conducted ventricular complexes, the markedly bizarre ventricular complexes and runs of ventricular flutter-fibrillation at X. The plasma procaine amide level was 29.0 mg. per L., potassium 3.28 and sodium 148.0 mEq. per L. Infusion of 60 mEq. of molar sodium lactate was started at the end of this strip.

E. Five minutes after *D*, note the increase in the blood pressure (85/30), the restoration of normal sinus rhythm, and decreased width of the QRS complexes (a decrease from 0.20 to 0.12 sec. at X) in comparing the QRS complexes in the initial to the terminal portion of the strip. The plasma procaine amide level has decreased to 24.7 mg. per L., potassium is 2.89 mEq. per L. and sodium is now 156.5 mEq. per L.

caine amide, like quinidine, increases the refractory period of the atrium, prolongs conduction, and paralyzes the vagus; it also increases the refractory period of the ventricle. The toxic effects of procaine amide consist in the development of hypotension and the production of certain electrocardiographic alterations. These consist in alteration of the T waves, prolongation of the QT segment, slight PR interval prolongation and widening of the QRS complexes, and alterations in rhythm similar to those produced by quinidine. QRS widening requires precautions in therapy similar to those following the administration of quinidine. When the QRS width increases over 25% of the control value or if the QRS exceeds 0.14 sec., further administration should be stopped or one should proceed with great caution under continuous electrocardiographic control. Infusions continued beyond this point usually result in the occurrence of a slow ventricular flutter and ventricular fibrillation. McClendon, Hansen and Kinsman[5] observed that procaine amide exerts a major effect through a primary myocardial depressant action. They studied the hemodynamic changes in normal and dis-

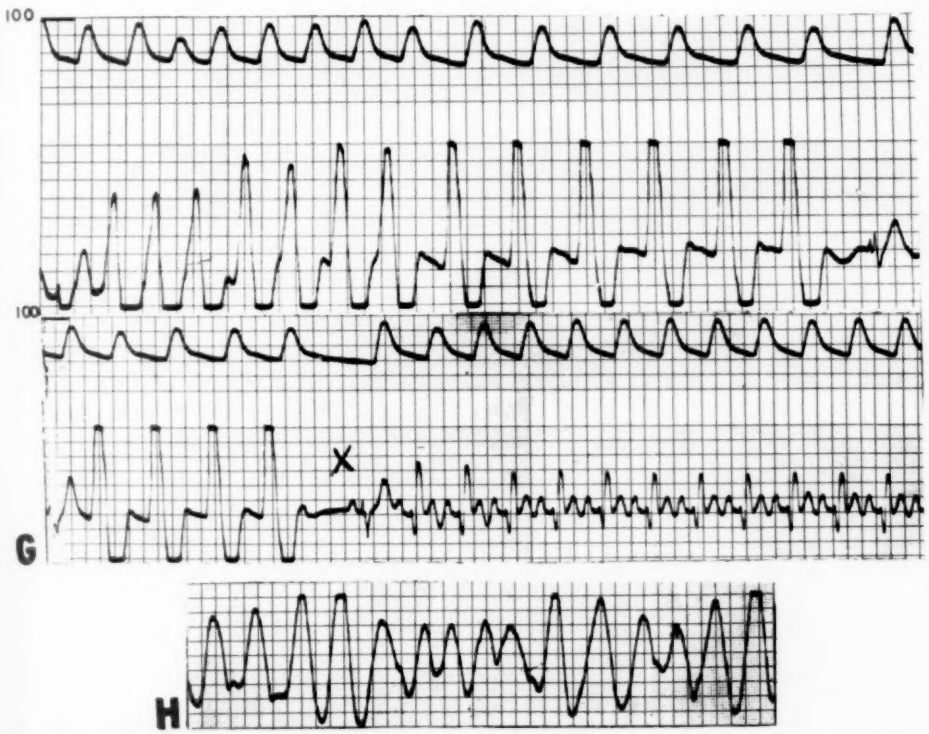

Fig. 4*b*.—*F*. Twenty minutes after *E* and also during the administration of molar sodium lactate. The ventricular complexes narrowed from 0.24 to 0.12 of a second.

G. Continuous tracing recorded during the intracardiac administration of 10 mEq. of molar sodium lactate into the left ventricle. Note the conversion of a ventricular pacemaker to a normal sinus rhythm at X.

H. Finally, the dog died in ventricular fibrillation after 3 hours of constant procaine amide infusion.

eased human hearts and observed a fall in cardiac output, increase in blood flow from the pulmonary vascular bed, and a fall in pulmonary artery pressure. These changes were most pronounced in patients with diseased hearts and less evident in normal hearts. Mitchell and Jacoby[6] observed that procaine amide toxicity is increased by blood acidosis and decreased by alkalosis. Regan and associates[7] observed that procaine amide blocked the uptake of sodium by the heart. This may be the result of a diminution of K flux from the myocardial cells.

The mechanisms of the depressant action of procaine amide on the heart have not been as extensively studied as those of quinidine (Holland[2,3]). Because of the similarity in cardiac effect it is quite likely that many of the actions on depression of oxygen uptake and enzymatic activity may be similar to those of quinidine (Bellet *et al.*[1]).

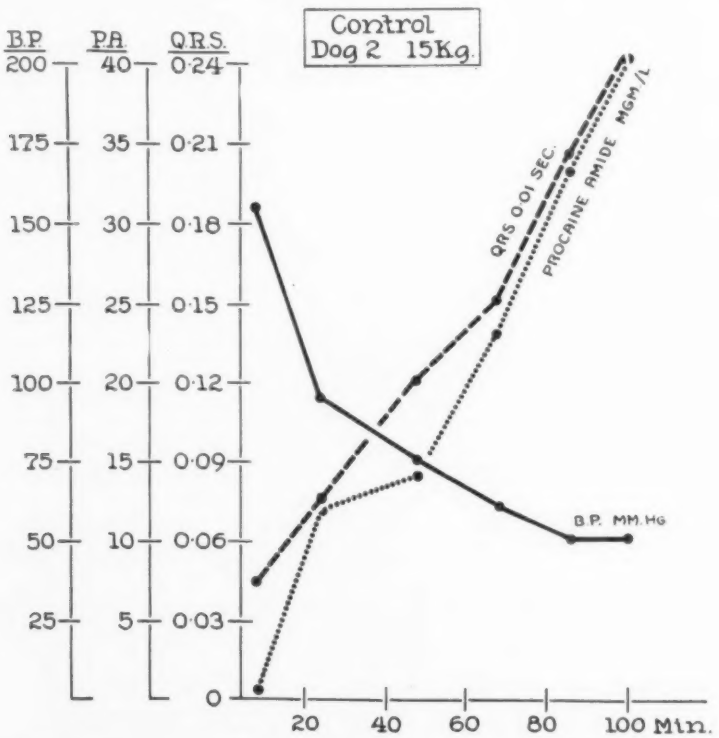

Fig. 5.—Effects of procaine amide infusion upon the procaine amide levels, width of the QRS complexes, and blood pressure.

The ordinates indicate the width of the QRS complexes, the blood pressure and plasma quinidine levels, respectively. The abscissae represent the time periods in minutes, during which procaine amide was administered. Note the increase in the width of the QRS complex, and the fall in blood pressure as blood procaine amide level increases.

The increase in the width of the QRS complex almost parallels the increase in blood procaine amide levels.

The dog finally died after 100 min. of infusion at a blood procaine amide concentration of 40 mg. per L. when the width of the QRS was approximately 0.24 second. There was a sudden fall of the blood pressure to zero during this terminal stage.

Moreover, Holland[3] presented evidence that procaine amide produced its effect on the mechanism of the isolated atrium by depressing the outward flux of K ions (Holland[2]). This effect was later shown to be operative for quinidine as well (Holland[3]).

MECHANISMS OF MOLAR SODIUM LACTATE EFFECTS. The reversal of the cardiotoxic effect of procaine amide by molar sodium lactate is of considerable interest. We are uncertain as to all of the factors involved in the reversal of the observed cardiotoxic effects. The

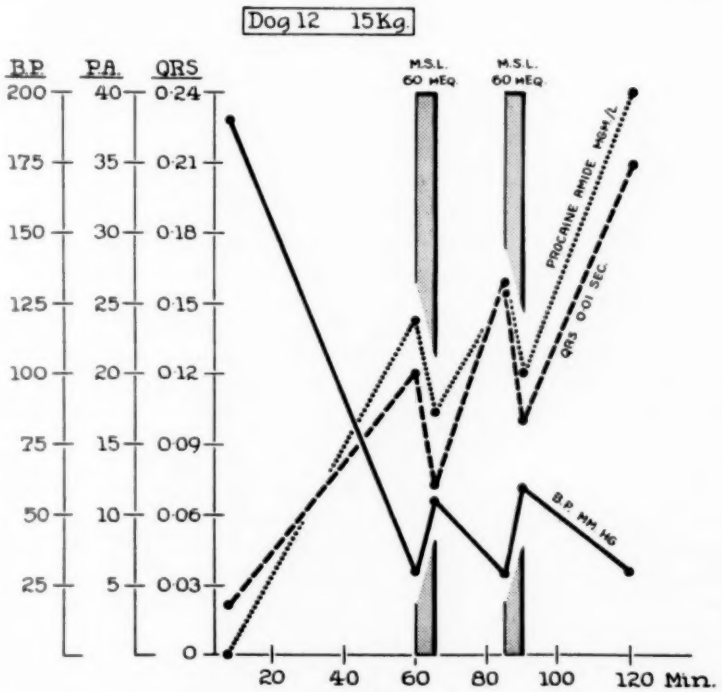

Fig. 6.—The effect of molar sodium lactate on blood procaine amide levels, width of the QRS complexes and blood pressure.

The ordinates indicate the width of the QRS complexes, the blood pressure and plasma procaine amide levels, respectively. The abscissae represent the time periods in minutes during which procaine amide was administered. Note the characteristic effects of procaine amide infusion. There is a fall in blood pressure, an increase in the width of the QRS complexes and an increase in the blood procaine amide concentration after 60 minutes of continuous procaine amide infusion. At this time 60 mEq. of molar sodium lactate was infused over a period of 5 minutes. Note the increase in the blood pressure, a decrease in the width of the QRS from 0.12 to 0.07 of a second, and a decrease in blood procaine amide concentration from 24 mg. per L. to 17 mg. per L.

With the continuance of the procaine amide infusion there is again an increase in blood procaine amide concentration resulting in a fall in blood pressure and an increase in the width of the QRS complex. After 85 min. of procaine amide infusion, 60 mEq. of molar sodium lactate was again infused. This resulted in an increase of the blood pressure from 60 to 120 mm. Hg., a decrease in the width of the QRS from 0.16 to 0.10 of a second, and a decrease in blood procaine amide level from 26 to 20 mg. per L.

The dog finally died in ventricular fibrillation after 120 minutes of continuous procaine amide infusion at a blood procaine amide level of 40 mg. per L.

mechanisms of the action of molar sodium lactate may be due to the following factors: a) decrease in plasma procaine amide concentration, b) decrease in the potassium level and shift of the pH to the alkalotic side and c) the effect of the lactate. These effects are apparently similar to those described during quinidine toxicity (Bellet *et al.*[1]).

Summary. The therapeutic effect of molar sodium lactate during procaine amide toxicity was studied in two groups of dogs: Group 1 in which continuous procaine amide infusion was given until death of the animal; Group 2 prepared in a manner similar to Group 1 in which the effects of molar sodium lactate were studied at various stages of procaine amide toxicity.

The electrocardiographic abnormalities and the hypotension which resulted from procaine amide toxicity were consistently and markedly improved by the use of molar sodium lactate.

Molar sodium lactate was effective in reversing the cardiotoxic effects of procaine amide toxicity at a more advanced stage than that observed with quinidine.

Infusion of procaine amide (in addition to its increased concentration in the blood) results in profound electrolyte changes consisting of the production of acidosis as manifested by a decreased pH and CO_2; in addition there was a decrease in potassium, calcium and magnesium.

The beneficial effects of molar sodium lactate in procaine amide toxicity are suggested to result from a combination of the following factors: a) decrease in the plasma procaine amide levels, b) improvement of the acidosis, c) decrease in serum potassium and d) the effect of lactate as a metabolic fuel.

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SUMMARIO IN INTERLINGUA

Un Reversion Del Effectos Cardiotoxic De Procainamido Per Molar Lactato De Natrium

Le effecto therapeutic de molar lactato de natrium ni toxicitate per procainamido esseva studiate in duo gruppos de canes. In le prime gruppo, continue infusion de procainamido esseva administrate usque al morte del animal. In le secunde gruppo le animales esseva preparate in le mesme maniera, sed le effectos de molar lactato de natrium esseva studiate a varie stadios del toxicitate a procainamido.

Le anormalitates electrocardiographic e le hypotension que resultava ab le toxicitate per procainamido esseva meliorate uniforme- e marcatemente per le uso de molar lactato de natrium.

Molar lactato de natrium esseva efficace in reverter le effectos cardiotoxic de procainamido a plus avantiate stadios que in le caso del effectos cardiotoxic de quinidina.

Le infusion de procainamido resulta—a parte le augmento de su concentration in le sanguine—in profunde alterationes electrolytic. Le resultante production de acidosis es manifeste in un reduction de pH e un diminution de CO_2. Esseva etiam constatate un reduction de kalium, de calcium, e de magnesium.

Es suggerite que le effectos benefic de molar lactato de natrium in toxicitate per procainamido resulta ab un combination del sequente factores: (a) Le reduction del nivellos de procainamido in le plasma, (2) un melioration del acidosis, (c) un reduction del kalium in le sero, e (d) le effecto de lactato como combustibile metabolic.

SUMMARIO IN INTERLINGUA

(See page 165 for original article)

Le Reversion Del Effectos Cardiotoxic De Quinidina Per Molar Lactato De Natrium

A causa del similitude inter le effectos cardiotoxic de quinidina e illos de hyperkaliemia e a causa del effectos benefic de molar lactato de natrium in le reversion del cardiotoxicitate de kalium, le effectos de molar lactato de natrium esseva studiate in canes in stato de cardiotoxicitate per quinidina.

Le animales experimental esseva dividite in duo gruppos. In un del duo, *i.e.* le gruppo de controlo, gluconato de quinidina esseva administrate per infusion continue usque le subjecto moriva. In le secunde gruppo, molar lactato de natrium esseva administrate a varie stadios del toxicitate de quinidina.

Le effecto cardiotoxic de quinidina, in tanto que illo se manifestava in hypotension e in alterationes del electrocardiogramma, esseva revertite per le administration de molar lactato de natrium. Iste reversion poteva esser observate repetitemente. Tamen, in le multo avantiate stadios de cardiotoxicitate, in que un lente rhythmo idioventricular esseva presente e in que le tension del sanguine esseva presso al nivello de zero, le uso de molar lactato de natrium esseva minus efficace o non efficace del toto.

Es opinate que le effectos benefic de molar lactato de natrium es causate per le sequente factores: (a) Reduction del concentration de quinidina in le plasma, (b) reduction del kalium in le sero, con transition del pH al latere alcalotic, e (c) utilisation directe del lactato como materia prime in le production de energia.

CLINICAL RESULTS WITH METHOCARBAMOL* IN OPIATE WITHDRAWAL

By Arnold H. Zucker, M.D.†

(From the U.S. Public Health Service Hospital, Fort Worth, Texas)

The methadone substitution method of withdrawal has been proven effective in relieving the more severe manifestations of the opiate withdrawal syndrome (Fraser and Grider[1]). In this method the presence of physical dependency on opiates is determined by withholding all drugs until definite signs of the opiate withdrawal syndrome are noted. After this physical dependency is established, syrup of methadone is substituted for the drug of use in sufficient quantities to control the signs of withdrawal, the amount being determined by a standardized empirical method (Zucker, Machlin and Scott[5]). Once the stabilization dosage is established, the addict is maintained on this amount of methadone for a few days and then withdrawn over a period averaging 10 days. This method of treatment is based on the facts that methadone will prevent the appearance of signs of abstinence from any known opiate and that abstinence from methadone is milder than abstinence from any of the other commonly used opiates.

Evident, however, is some degree of discomfort. Anorexia is very common during the early phase, but the return of appetite is spontaneous and rapid. Insomnia is almost universal and bedtime sedation is frequently required. Almost all addicts complain of some muscular pain, in the form of "aching," "drawing," and "tightness." About one-third of the addicts demonstrate some degree of increased muscle tension, in the form of twitching, fibrillation, or spasm. To counteract this symptom, various propanediol derivatives have been used. At the withdrawal ward of the United States Public Health Service Hospital, Fort Worth, Texas, there has been occasion to observe results with mephenesin (Tolserol), meprobamate (Miltown), and methocarbamol (Robaxin).

Mephenesin was first used routinely for all patients with muscular symptoms. Approximately 200 patients were placed on regimens of 1 gm. 4 times daily for periods averaging 10 days. Although the results were not quantified, dissatisfaction led to trials of the newer derivatives. At most, 25% of patients responded favorably to mephenesin and the relief was rarely sustained. A controlled evaluation of meprobamate was then carried out (Zucker, Machlin and Scott[5]). In this double-blind study 60 patients received the methadone substitution method of withdrawal. One group of 20 patients received meprobamate, a second group of 20 patients received an inert placebo, and the remaining 20 patients served as controls. The meprobamate group demonstrated twice the incidence of increased objective muscle tension as the controls. They also manifested significantly more

*The methocarbamol used in this study was supplied as Robaxin by A. H. Robins Company, Inc., Richmond, Virginia.

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subjective muscle tension as compared with the control group. The increase in subjective complaints was attributed to the negative placebo effect observed in this study, the placebo group responding in a similar manner as compared with controls. This effect was felt to contribute to the increase in objective muscle tension, but a paradoxical physiological response to meprobamate in the opiate withdrawal syndrome was also hypothecated. Related to this response might be the reported locomotor stimulation effect of meprobamate in dogs and mice (Irwin and Unna[2]). In this study it was concluded that meprobamate is not of value as an adjunct in the management of opiate withdrawal.

Procedure. Methocarbamol was used on a group of 30 patients complaining of moderate to severe muscular symptoms, according to the rating scale which will be described. Although complaints of muscular pain were almost universal, a contemporary group had only mild symptoms and were not used in this study. In all patients the abstinence signs were adequately controlled with methadone, except for the residua described above. Of the experimental group, 19 were addicted to heroin, 4 to morphine, 2 each to Dilaudid and Demerol, one each to paregoric, codeine and methadone. In general, the experimental group represented those addicts with a more severe physical dependency, who would be expected to have more discomfort during withdrawal. Most of them experienced some anorexia and insomnia as well as muscular pains, but were otherwise reasonably comfortable. All were treated with the standardized methadone substitution method of withdrawal. A dosage of 1.0 gm. 4 times daily of methocarbamol for periods averaging 10 days was given. Control patients were not used in this series, the previous experiences being used as a rough baseline for comparison. Muscle tension, objective, was evaluated according to a 3-point scale: 0 = No evidence of any discomfort. Examination of muscles revealed no twitching, fibrillation nor muscle spasm. 1 = Evidence of moderate discomfort. The patient might sleep on the floor or a hard surface and curl himself into odd positions. Palpation of muscles revealed the presence of definite muscle spasm. 2 = Evidence of marked discomfort. There might be twitching and kicking motions of the extremities. Palpation revealed the presence of severe muscle spasm and tenderness. Muscle tension, subjective, was evaluated according to a 4-point scale: The patient was asked, "How do you feel?" His responses were recorded as follows: If he replied to the question by complaining of severe muscle pains, he was rated as 3. A rating of 2 was recorded when the patient complained of mild muscle pain. If the patient did not respond with a complaint about his muscle symptoms, he was then asked, "Do you have any muscular pains?" If he responded to this by complaining of severe muscle pains, he was rated as 2. A rating of one was recorded when he complained of mild or moderate muscle pain. A completely negative response was rated as zero.

Results. Thirteen patients complained initially of severe (3) subjective muscle tension. The remaining seventeen patients were rated as having moderate (2) subjective muscle tension. A good response was recorded if patient demonstrated, within a few days, a change of at least 2 on the subjective muscle scale, that is, a minimal change in rating from 3 to 1 or 2 to 0. As noted in Tables 1 and 2, 18 of the 30 subjects responded with an improvement of this degree. When recorded, the response was within 3 days after administration of methocarbamol. It occurred on the first day in 2 cases, the second day in 6 cases and the third day in 10 cases. In all cases the relief lasted so long as the medication was given. As noted in Table 3, 10 of these responsive patients had objective evidence of increased muscle tension, in all cases a rating of one. All were recorded as zero within a 3-day period. Of the 12 patients with poorer subjective responses, 8 had evidence of increased muscle tension, all with a rating of one. This was observed in 3 patients after a 4-day period. There was no exact correlation between increased objective and subjective muscle tension, although patients with severe subjective

complaints usually had evidence of increased muscle tension. None of the 18 patients with a good subjective response reported post-withdrawal symptoms, a fairly common complaint. Typical reactions were: "These pills are loosening up my muscles." "The twitches stopped the day after I took the pills; my muscles feel relaxed."

TABLE 1.—MUSCLE TENSION, SUBJECTIVE

		Day of Medication				
Rating	*Initial*	*1*	*2*	*3*	*4*	
3 (severe)	13	8	3	2	2	
2 (moderate)		5	6	4	4	
1 (mild)			3	4	3	good
0 (negative)			1	3	4	results

TABLE 2.—MUSCLE TENSION, SUBJECTIVE

		Day of Medication				
Rating	*Initial*	*1*	*2*	*3*	*4*	
2 (moderate)	17	9	6	3	2	
1 (mild)		6	5	3	4	
0 (negative)		2	6	11	11	good results

TABLE 3.—MUSCLE TENSION, OBJECTIVE

			Day of Medication				
			0	*1*	*2*	*3*	*4*
Patients with Good Subjective Responses	18	Evidence of Objective Muscle Tension	10	8	3	0	0
Other Patients	12		8	7	4	4	3

Discussion. Opiates stimulate the reflex centers of the spinal cord. This hyperreflexia is apparently antagonized by the depressant action on higher brain centers. It has been postulated that muscle spasm in the opiate withdrawal syndrome may be the outcome when the initial depressant effects are decreased and rebound is increased (Wikler[4]). Mephenesin has been found to exert a depressant effect on the spinal cord. Truitt and Little[3] have demonstrated that methocarbamol produces a prolonged relaxing effect on skeletal muscle through a depression of multisynaptic pathways, its site of action being at the interneuronal junction. Results in this pilot study indicate that methocarbamol is effective in alleviating increased muscle tension during the opiate withdrawal syndrome. More extensive controlled studies are indicated.

Summary. Muscle spasm is a prominent finding in the opiate withdrawal syndrome. Some degree remains during treatment by the methadone substitution method of withdrawal. Various propanediol derivatives have been used to counteract this. Experiences with mephenesin and meprobamate were described; neither drug was consistently effective. Methocarbamol was used on a group of 30 opiate addicts undergoing withdrawal by the metha-

done substitution method and complaining of significant muscular pain. Results in this pilot study indicate that methocarbamol is effective as an adjunct in the alleviation of increased muscle tension during the opiate withdrawal syndrome. The hypothesized mode of action was described.

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SUMMARIO IN INTERLINGUA

Resultatos Clinic Obtenite Con Methocarbamol In Le Privation De Opiatos

Spasmos muscular es un constatation prominente in le syndrome del privation de opiato. Un certe grado de isto persiste durante le tractamento per le methodo de privation a substitution de methadona. Varie derivatos de propanediol ha essite usate como contra-agentes. Experientias con mephenesina e meprobamato es describite. Ni le un ni le altere esseva uniformemente efficace. Methocarbamol esseva usate in un gruppo de 30 toxicomanos durante privation de opiato per le methodo a substitution de methadona pro combatter le adverse effecto lateral de grados significative de delores muscular. Le resultatos del presente studio preliminari indica que methocarbamol es efficace como adjuncto in alleviar le augmentate tension muscular in le syndrome del privation de opiato. Le probabile modo de action del droga es describite.

ACUTE GRANULOCYTIC LEUKEMIA IN PREGNANCY: REPORT OF FOUR CASES, WITH APPARENT ACCELERATION BY PREDNISONE IN ONE

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Acute leukemia in pregnancy poses a delicate therapeutic problem, because the very agents which are ordinarily most effective in antileukemic therapy may seem contraindicated by virtue of their potential deleterious effects on the fetus (Smith, Sheehy and Rothberg[18]). Both folic acid antagonists and purine analogs are capable of inducing abortion and developmental anomalies if administered early in gestation. For this reason, and since a major aim of therapy in such cases is generally to secure normal progeny, there is considerable sentiment in favor of steroid hormones as opposed to any of the antimetabolites in the management of acute leukemia during pregnancy. In a recent comprehensive review of the subject (Yahia, Hyman and Phillips[20]), it was maintained that corticosteroids are the drugs of choice in acute leukemia during pregnancy, with antimetabolites reserved for patients in whom steroid control fails. The following cases are presented chiefly to illustrate that corticosteroids also may have their drawbacks in the therapy of acute granulocytic leukemia in the pregnant patient, and that therapy with an antimetabolite may be carried out with safety and a favorable result.

Case Reports. Case 1 (WRAH no. 281386). This 15-year-old housewife was admitted to another hospital in June, 1949, because of increasing weakness and fatigue for one month. Her last menstrual period was December 15, 1948. She was 5 months pregnant, and was extremely pale. The hemoglobin was 28% of normal; the white cell count was 33,500 per c.mm. with 90% young myeloid cells; and an iliac marrow aspirate was interpreted as acute granulocytic leukemia. She was given 3 transfusions and transferred to Walter Reed Army Hospital. Physical examination revealed a pregnant female with pallor, bleeding gums, numerous small hard cervical nodes, and a grade 2 precordial systolic murmur. Blood counts changed little during the next 3 months, except for the hemoglobin which varied with the frequently required transfusions; a typical count revealed 26,000 leukocytes per c.mm. with 40% blasts, 12% promyelocytes, 9% myelocytes, 3% metamyelocytes, 20% neutrophils, and 16% lymphocytes; and the platelets numbered 7000 per c.mm. The patient had repeated ecchymoses and epistaxes and bouts of hematuria. Therapy consisted of transfusions and penicillin, the latter given for presumed bacterial infection during episodes of fever. On August 26, she developed irregular uterine contractions and was transferred to the obstetrical service. Membranes were artificially ruptured and on

September 2, she spontaneously delivered a 2200 gm. macerated fetus. Fetal death was attributed to premature separation of the placenta; necropsy revealed no evidence of leukemic infiltration in placenta or fetus. The mother went into shock post partum; she revived with oxygen and 2 transfusions but finally succumbed 2 days later. She had received a total of 44 transfusions. No necropsy was performed on this patient.

adenopathy. Bone marrow examination revealed acute leukemia. The patient was transfused, and beginning on May 9, 1954, was placed on cortisone therapy. On May 15 she was transferred to Walter Reed Army Hospital where initial studies revealed a leukocyte count of 260,000 per c.mm. with 95% myeloblasts, and marrow aspiration confirmed the diagnosis of acute granulocytic leukemia. Mercaptopurine, 150 mg. daily, was

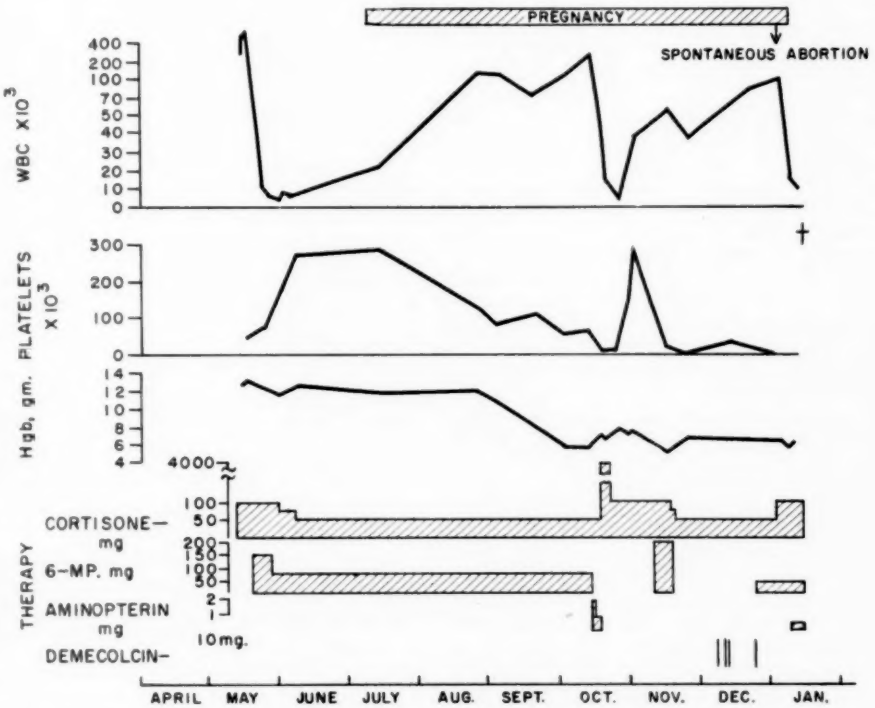

Fig. 1.—Hematologic data and therapy in case 2, a 22-year-old woman with acute granulocytic leukemia and pregnancy.

COMMENT. This case illustrates the typical course of untreated acute leukemia in pregnancy. Unless the disease has its onset late in pregnancy, the mother rarely survives long enough to deliver a viable infant.

CASE 2 (WRAH no. 3655059). This 22-year-old housewife (Fig. 1) was admitted to another hospital in April, 1954, because of cough and gross axillary adenopathy. Chest roentgenograms revealed massive mediastinal

added to the treatment regimen. The patient improved subjectively, the white blood cells fell to 5,000 per c.mm. and the spleen and lymph nodes decreased in size. On June 15, she was discharged from the hospital on a maintenance dose of 6-mercaptopurine, 75 mg. daily, and cortisone, 50 mg. daily.

On August 28, the patient was readmitted, having developed progressive weakness and fatigue, generalized adenopathy, and amenorrhea. Physical examination revealed, in addition to the adenopathy, the spleen to be palpable 13 cm. below the costal margin,

and the cervix consistent with pregnancy. The leukocytes numbered 127,500 per c.mm. with 91% blasts; the hematocrit was 38% and the platelets 124,000 per c.mm. On September 8, a test for pregnancy was positive. On October 14, therapy was begun with aminopterin, of which the patient was given a total of 8 mg. over the course of 6 days. Beginning October 17, "massive doses" of cortisone, 4 gm. daily, was given for 5 days. There followed a rapid fall in white count, and a transient rise in platelets. The patient developed severe diarrhea and, in November, extensive hair loss. On November 8, the peripheral white count was 49,800 per c.mm. with 4% blasts, 28% metamyelocytes and 54% segmented neutrophils, while the bone marrow remained characteristic of acute leukemia, with 85% blasts. The patient improved temporarily and was thereafter maintained on cortisone, 50 to 100 mg. daily. In December, five 10-mg. doses of demecolcin were given without apparent effect. Thereafter the patient worsened, with fever, malaise, anorexia, and increased adenopathy. Mercaptopurine therapy was resumed, but the patient's condition deteriorated further. On January 9, she spontaneously delivered a premature male infant, who lived for about 12 hours. There was little hemorrhage incident to delivery. Subsequently, the patient was given aminopterin, 0.5 mg. daily, in addition to the other medications. Despite a fall in the white count from 96,000 to 11,200 per c.mm., the patient became progressively weaker and she expired on January 14, 1955.

At necropsy, the patient had multiple ecchymoses and subconjunctival hemorrhages. Cervical, submaxillary, supraclavicular, axillary, mediastinal, peribronchial, and mesenteric lymph nodes were all extremely large, firm and prominent. Microscopically, they showed obliteration of normal architecture with replacement by immature cells resembling myeloblasts; and areas of extramedullary hematopoiesis. About 100 ml. of blood-tinged fluid was present in each pleural space. The heart was unremarkable; the lungs showed a mild lobular pneumonia, and a low grade interstitial infiltration with immature leukocytes. The peritoneum contained about 50 ml. of blood-tinged fluid, and its lining contained many petechial hemorrhages. The liver weighed 2680 gm., and microscopically showed central congestion, foci of necrobiosis, and infiltration with immature cells in periportal areas; areas of extramedullary hematopoiesis were present; and sinusoidal lining cells were prominent. The spleen weighed 1504 gm. and was infiltrated with myeloblasts; reticuloendothelial cells were prominent, and there was a small splenic infarction. Stomach and intestines showed many submucosal hemorrhages and a small amount of intraluminal blood. The kidneys were normal. The uterus weighed 820 gm., and showed hypertrophy of muscle fibers, dilatation of blood vessels and areas of hemorrhage within the myometrium; there was a questionable mild leukemic infiltration. The ovaries were unremarkable and showed no leukemic infiltration. The central nervous system was grossly normal, but leukemic infiltration of the meninges was prominent microscopically.

The infant died of respiratory difficulty. At necropsy, he showed the features of prematurity, and weighed 730 gm. There was no evidence of leukemia. There were no malformations; and the only abnormality was in the lungs, which showed severe bilateral atelectasis.

COMMENT. There are several points of interest in this case. First, this patient conceived while on 6-mercaptopurine; but despite this fact, and the prolonged use of both 6-mercaptopurine and cortisone, plus 2 courses of aminopterin and a trial of demecolcin, her child was free of any malformation. Second, although the simultaneous use of several drugs makes it impossible to attribute either of the patient's 2 remissions to any one agent with certainty, it is clear that cortisone was at least not harmful to the patient and was probably beneficial. Finally, one may speculate whether the peripheral blood picture simulating chronic granulocytic leukemia, which obtained in November, 1954, may have been in part a consequence of the steroid therapy.

CASE 3 (WRAH no. 4521019). This 35-year-old housewife (Fig. 2) was admitted to another hospital on May 7, 1957, because of purpura and fatigue for one month. She was in her second pregnancy, her last menstrual period having been December 3, 1956. The white blood cell count was 15,600 per c.mm. with 84% "abnormal lymphocytes." A week later, it was 23,550 per c.mm. Bone marrow aspiration revealed leukemia. The patient was given 2 transfusions and transferred to Walter Reed Army Hospital. On admission, the pa-

tient was in no distress except for easy fatiguability and occasional headache; she was ambulatory on the ward. Physical examination revealed a pale woman with a 5-month pregnancy and scattered ecchymoses. There was moderate cervical adenopathy and the spleen tip was felt 2 cm. below the costal margin. On May 18, the hemoglobin was 10.2 gm. per 100 ml.; and the leukocytes numbered 33,000 per c. mm. with 62% blasts, 27% promyelocytes, 7% lymphocytes and 1% neutrophils. The platelet count was 23,000 per c.mm. Sternal marrow aspirate was hypercellular and contained 97.5% myeloblasts. On May 23 therapy was begun with prednisone, 660 mg. per day. On May 25, the patient began to complain of aching pains in both arms and legs and in her back; pain was relieved only partially by moderate doses of aspirin and codeine. By May 27, generalized bone pain was persistent and had become severe enough to require hypodermic injection with Demerol. At this time, the leukocyte count had risen to 156,000 per c.mm. with 98% blasts and the platelets to 46,000 per c.mm. On May 28, there was exquisite bony tenderness. Thereafter pain was controlled by frequent injections of morphine and chlorpromazine.

Because of the aggravation of this patient's disease following institution of steroid therapy, it was decided to taper and discontinue the prednisone, and treatment with 6-mercaptopurine, 175 mg. per day was begun. However, at 6:00 a.m. on May 31, the patient vomited, and thereafter she was unresponsive except to painful stimuli. Stertorous Cheyne-Stokes respiration was present. The right eye was miotic and fixed in lateral gaze. The right arm and both legs were flaccid. There was hyperreflexia in the right arm, but knee, ankle, and plantar reflexes could not be elicited. An airway was inserted and the patient was placed in an oxygen tent. The white cell count had risen to 193,000 per c.mm., while the platelets had fallen

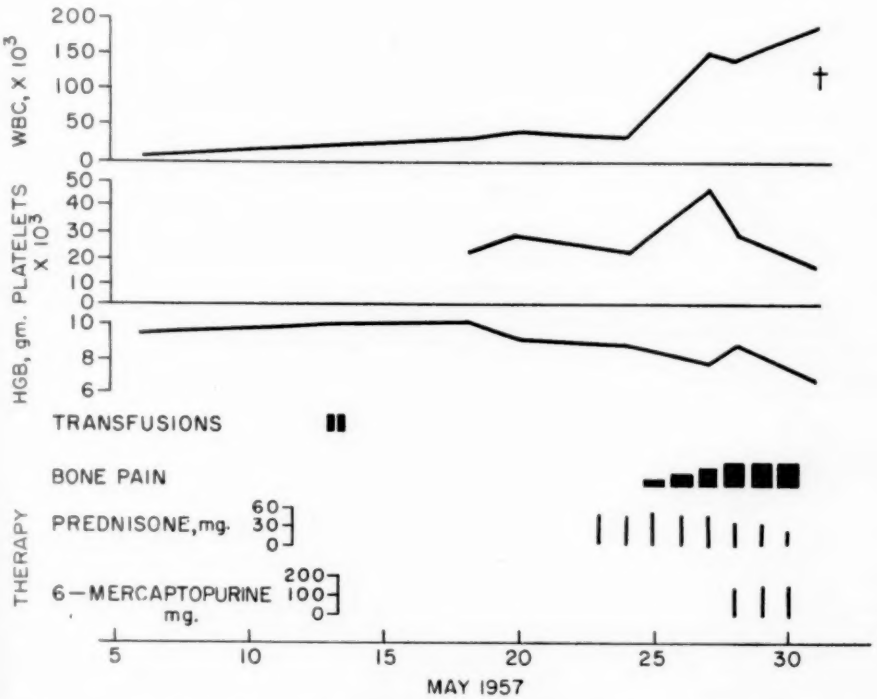

Fig. 2.—Hematologic data and therapy in case 3, a 35-year-old woman with acute granulocytic leukemia and pregnancy.

to 17,000 per c.mm. The patient's breathing became more irregular, and flaccid paralysis became generalized. At 11:13 a.m. respiration ceased. At 11:15 heart action and pulse could no longer be heard, and a postmortem Caesarean section was carried out, with delivery of a 995 gm. immature male infant.

The infant was placed in an incubator, but respiration remained gasping and irregular until he finally died 2 hours after delivery. Postmortem examination revealed immaturity, bilateral pulmonary atelectasis, and no evidence of leukemia.

Necropsy performed on the mother revealed pallor and ecchymoses of the skin. Normal changes of pregnancy were evident in the breasts, uterus and endocrine glands. Lymph nodes were slightly enlarged and their normal architecture was replaced by leukemic infiltration. The heart contained multiple small petechiae. The lungs contained bilateral apical pleural scars and focal areas of atelectasis and hemorrhage. The liver weighed 3220 gm. and showed leukemic infiltrates in portal spaces, around central veins and in the sinusoids. The spleen weighed 1210 gm.; it contained many small infarcts and its normal architecture was replaced by leukemic infiltration. The kidneys showed hemorrhages into the calyces and a few small areas of leukemic infiltrate around the large vessels. The uterus contained a large fresh incision; the myometrium was infiltrated by leukemic cells. The ovaries were unremarkable. The bone marrow was densely packed with uniform sheets of myeloblasts. The brain was swollen and congested, especially on the left, and there was a large hemorrhage involving the entire left temporal lobe and the anterior portion of the left occipital lobe, with rupture into the inferior horn of the left lateral ventricle.

COMMENT. In this patient, the administration of prednisone was associated with a dramatic acceleration of the leukemic process, manifested by a rapid rise in the leukocyte count and severe bone pain. The possibility that this acceleration was attributable to the steroid therapy is discussed below.

CASE 4 (WBAH no. TR-416). This 33-year-old housewife (Fig. 3) was admitted to William Beaumont Army Hospital on January 25, 1958, because of fever and cervical adenopathy of 2 weeks' duration. She was about 4 months pregnant, the last menstrual period having been in September, 1957. Physical examination revealed a pale, chronically ill woman in the fourth month of pregnancy. Oral temperature was 100°. There was moderate cervical submandibular, and axillary adenopathy. The liver edge was at the costal margin and the spleen was 4 cm. below the costal margin. The hemoglobin was 9.0 gm. per 100 ml. The white cells numbered 33,500 per c.mm. with marked immaturity of the granulocytic series, including 5% blasts and 34% "basket cells." Platelets were decreased on the blood smear. An iliac aspiration revealed the marrow to be hypercellular with 93% myeloblasts, 4% metamyelocytes, 2% lymphocytes, and 1% eosinophils. The patient was given tetracycline, 1 gm. daily, and 2 whole blood transfusions. Her fever subsided and appetite and strength increased. She was discharged home on a regimen of ferrous sulfate 300 mg., t.i.d., and a multiple vitamin preparation.

The patient's adenopathy persisted and easy fatiguability gradually returned. On February 13 she was readmitted to the hospital. The spleen was now 4 cm. below the costal margin. The hemoglobin was 8.3 gm. per 100 ml., and the white blood cell count was 150,000 per c.mm. with 91% blasts, 4% myelocytes, and 6% stabs. On February 14, therapy was begun with 6-mercaptopurine, 150 mg. per day, and she was discharged from the hospital on the following day.

On February 17, the leukocyte count was 201,000 per c.mm.; by February 24, it had fallen to 110,000. Four days later, the white cell count was 1800 per c.mm. with 9% neutrophils, 28% immature myeloid cells and 63% lymphocytes. The hemoglobin was 9.0 gm. per 100 ml. and the platelets appeared normal in number on the smear. On the same date, the patient complained of chills, sore throat, and her temperature was 104.8°, and she was again hospitalized. By this time the uterus had increased to 5-month size, and fetal movements were present. Lymphadenopathy and splenomegaly had decreased. Mercaptopurine was immediately stopped, and the patient was given a total of 1250 ml. of whole blood during her 6-day hospitalization. The patient was treated with antibiotics and became afebrile within 24 hours. On March 6 the white cells had risen to 2700 per c.mm. with a few immature cells and the patient was discharged from the hospital.

By March 24 the leukocytes had increased to 40,700 per c.mm. with many immature cells; and 6-mercaptopurine was resumed in a dose of 100 mg. daily. On April 7 the white cell count had fallen to 17,000 per

c.mm. and the dose of 6-mercaptopurine was decreased to 50 mg. daily. During the next two months the leukocyte counts ranged from 4300 to 12,500 per c.mm. and the dose of 6-mercaptopurine was varied between 25 and 50 mg. daily. The patient remained asymptomatic and her pregnancy progressed uneventfully. There was marked diminution in lymphadenopathy and the spleen became impalpable; however, the enlarging uterus made delineation of the spleen difficult. On a 6 pound, 9¾ ounce normal male infant. No abnormal bleeding was noted. Physical examination following delivery revealed that the spleen remained 4 cm. below the costal margin. The patient was maintained on 50 mg. daily of 6-mercaptopurine during the postpartum period. She received no antibiotics during or following delivery and had no infection of any type. She elected not to nurse the baby and was discharged 5 days after delivery.

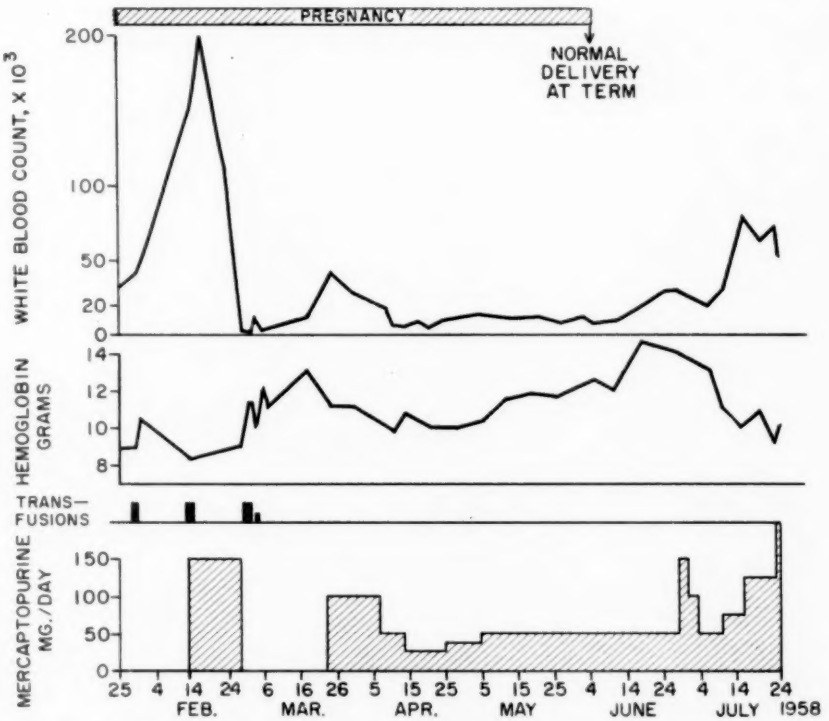

Fig. 3.—Hematologic data and therapy in case 4, a 33-year-old woman with acute granulocytic leukemia and pregnancy.

May 26, the white blood cell count was 8000 per c. mm., with 74% neutrophils, including rare immature forms, and 24% lymphocytes. Platelets appeared normal on smears, and clot retraction was normal.

On June 4 the patient entered the hospital in labor, which was short-lived, subsiding within an hour. On the following day spontaneous labor resumed, and after a 3-hour first stage and 25 minute second stage, with scopolamine, Demerol and pudendal block with xylocaine, the patient delivered

The infant had a vigorous cry at birth, did well in the neonatal period, and weighed 6 pounds, 8½ ounces on his fifth day of life. A careful physical examination disclosed no abnormalities. On the day of delivery, his hemoglobin was 17.4 gm. per 100 ml.; the white blood cell count was 7700 per c.mm. with 45% neutrophils, 48% lymphocytes and 7% eosinophils. There was polychromasia, and 8 nucleated red blood cells per 100 white cells. No immaturity of the white cells was noted. Tibial marrow aspiration obtained on

the same day showed 2% myeloblasts, 3% promyelocytes, 14% myelocytes, 11% metamyelocytes, 12% band forms, 5% segmented neutrophils, 3% eosinophils, 4% lymphocytes, 4% proerythroblasts, 17% erythroblasts, and 25% normoblasts. The M:E ratio was 1.1. At age 6 weeks, the infant was healthy and his blood counts were normal.

The mother continued to do reasonably well, on a maintenance dose of 50 mg. of 6-mercaptopurine daily. On June 18, the hemoglobin was 14.6 gm. per 100 ml.; and the white cell count was 16,900 with 65% neutrophils, including 2% band forms, and 34% lymphocytes. However, a second iliac marrow aspiration on the same date was hypercellular with 90% blasts, many mitoses, and an E:M ratio of 15. On June 28, the patient was hospitalized for a few days because of increasing leukocytosis, splenomegaly, and lymphadenopathy. Subsequently the dose of mercaptopurine was increased, but the white cell count continued to rise and the spleen and lymph nodes remained large. On July 26, the patient was again hospitalized. Her hemoglobin was 10 gm. per 100 ml., and the white blood cells numbered 53,300 per c.mm. with 100% blasts. The platelet count was very low, and the patient had numerous petechiae.

COMMENT. Because of the unfavorable experience with steroid therapy in case 3, it was decided to treat this patient with 6-mercaptopurine only. This agent was given during the last 4 months of pregnancy. The patient bore her pregnancy well, and had a full-term normal delivery. There was no evidence of any deleterious effect on the fetus. The only evidence of drug toxicity was a marked leukopenia during the initial phase of therapy, associated with an acute febrile episode; this was controlled by omission of the 6-mercaptopurine and institution of antibiotic therapy.

Discussion. Interpretation of factors affecting the outcome of a particular case of acute leukemia may be difficult because of the poor prognosis and fatal outcome of all cases. Even with optimal therapy, the median life span of adults with this disease is but 7 months, and only 10% of patients live as long as 16 months (Burchenal and Krakoff[4]); so it is not surprising that during the 9 months of pregnancy, with all its attendant stresses, most women with acute leukemia succumb. Yahia, Hyman and Phillips[20] have tabulated the cases reported in the English literature between 1944 and 1956. Of 20 pregnant patients whose acute leukemia appeared in the first or second trimester, only 8, or 40%, were able to survive the pregnancy, and most of these patients died shortly thereafter. The median survival time of these 20 patients was about 5 months, a figure which is probably not significantly different from that of nonpregnant patients in the same age group. Thus there is little effect of pregnancy *per se* upon acute leukemia, except that few women with the disease are able to survive the normal period of gestation.

One might also inquire as to the effect of the leukemia on the pregnancy. The high maternal mortality is due to the major terminal complications of leukemia, namely infection and hemorrhage. Premature labor is common, and prematurity is a principal cause of the high fetal mortality. Excessive postpartum hemorrhage occurred in 6 of the 32 cases tabulated by Yahia, Hyman, and Phillips[20]. The fetal mortality in their series was 39%.

The question of transplacental transmission of leukemia has been discussed by several authors. The clinical and pathologic data in our 4 cases provide additional evidence that such transmission does not occur. However, because of the possibility that the manifestation of leukemia in the offspring might be delayed, we would agree with Bierman *et al.*[2] that long-term follow-up of children born of leukemic mothers is desirable.

In view of the dismal outlook for the pregnant woman with acute leukemia,

it is understandable that patients with the disease are usually discouraged from becoming pregnant. However, occasionally pregnancy will occur nonetheless, as in our case 2. (If there is diminished rate of conception among leukemic patients, it is probably on the basis of general debility and limitation of sexual activity, rather than leukemic infiltration of the female genital organs.) More commonly, onset of pregnancy antedates the onset of leukemia. In either circumstance, the physician's aims in management may be governed to some extent by social and psychological factors peculiar to each case. Certainly, on purely physical grounds there does not appear to be any justification for therapeutic abortion in most cases. In general the aim of therapy is to sustain the pregnancy long enough to permit pelvic delivery at term, and the birth of a healthy infant. Caesarean section should be reserved for situations in which the mother is moribund, or for fetal distress in the presence of a viable gestation (Gillim[7], Yahia, Hyman and Phillips[20]).

In general, then, fetal salvage is a major objective in therapy of the pregnant leukemic patient. It is reasonable to inquire what plan of management is most likely to achieve this result. In the case of the antimetabolites, there is considerable evidence that under certain circumstances these agents may be harmful to fetal growth and development. This evidence has been reviewed in detail elsewhere (Smith, Sheehy and Rothberg[18]). Suffice it to say that unless the antimetabolite is given during the critical period of differentiation and organogenesis early in gestation, there is no evidence of any deleterious effect of ordinary therapeutic doses on the fetus. If institution of treatment of the pregnant leukemic patient can be deferred until after the first trimester, the possibility of teratogenesis should not influence the choice of therapeutic agent. This choice must therefore be made on other grounds.

STEROID ACCELERATION PHENOMENON. A number of authors have recently pointed out the possibility of acceleration of myeloid leukemia by steroid therapy. Rosenthal *et al.*[14] reported that 2 of 5 adults with acute granulocytic leukemia were apparently made worse by ACTH or cortisone. Fessas *et al.*[5] reported that 2 of 3 patients of ages 11 to 20 with acute granulocytic leukemia and 5 out of 8 in the adult group showed exacerbation of the disease shortly after institution of steroid therapy. They concluded that the steroids are not helpful in myeloblastic (and monoblastic) leukemia, and may be harmful, at least in adults. Björkman[3] described 3 patients with acute leukemia and one with erythromyelosis in whom administration of ACTH or cortisone was followed by rapid increase in peripheral blood myeloblasts; in 2 patients, this was associated with clinical deterioration. Thompson and Mackay[19] reported another such case. Joseph and Levin[8] described a 10-year-old boy with acute monoblastic leukemia and diabetes insipidus; on 2 separate occasions, the administration of cortisone was associated with onset of polyuria and polydipsia and a prompt rise in circulating leukocytes and blast cells. Necropsy revealed leukemic infiltration of the posterior lobe of the pituitary, and focal necrosis of the anterior lobe. Bierman[1] states that "at least 10% of patients with granulocytic leukemia both chronic and acute will develop exacerbations of their disease following the use of cortisone or ACTH." Ranney and Gellhorn[13] mention one patient with acute and 2 with subacute leukemia in whom the administration of massive doses of prednisone was associated with possible acceleration of the leukemic process. One

of their patients had myelomonocytoid leukemia; in the others, the type was unspecified. As these authors emphasize, clinical deterioration of a leukemic patient on corticosteroid therapy obviously does not prove an etiologic relationship. If the disease is unaffected by therapy, then it will pursue its natural course; and the natural course of leukemia implies rapid deterioration in a certain percentage of cases.

In many of the reported cases, the chief evidence for "steroid acceleration" has been simply an increase in the number of white cells and blasts in the peripheral blood. Progressive anemia, thrombocytopenia, organ enlargement, and clinical deterioration are not often described. It could therefore be argued that the observed peripheral blood changes are not necessarily an indication of true progression of leukemia, but may represent merely a nonspecific release of cells from the bone marrow. Case 3 of the present series, on the other hand, appears to provide more definite evidence of acceleration of leukemia. The patient's course had been relatively stable for 4 weeks prior to institution of steroid therapy. However, immediately after the prednisone was begun, not only did the number of immature cells in the blood rapidly increase, but the hemoglobin concentration and platelet count fell, and bone pain was strikingly increased. Observations on change in spleen size could not be reliably made because of the gravid uterus. The death of the patient from cerebral hemorrhage unfortunately precluded the opportunity to look for reversibility of the proliferative process on withdrawal of steroids.

Although the proof is not conclusive, it would appear that the present case is another example of the acceleration of acute myeloblastic leukemia by corticosteroid therapy. One can only speculate as to the mechanism of such an effect. There is evidence of a "myelostimulatory effect" of corticosteroids in the nonleukemic subject. Neutrophilia has been repeatedly observed after administration of steroids of ACTH, both in patients with arthritis and other diseases (Finch *et al.*[6]), and in normal subjects (Kowalski, Reynold and Rutstein[9], Nelson *et al.*[11]). Two features suggest that where there is no primary bone marrow disease, the neutrophilia may be the consequence of redistribution of cells rather than increased production of granulocytes. First is the fact that the neutrophilic leukocytosis in normal persons is manifest within 4 hours after the administration of the steroid, probably too soon for increased production to come into play. More impressive is the observation of Rosenthal, Etess and Litwins[15] who found no change in the morphology of aspirated marrow in 12 subjects before and after 7 days of administration of ACTH or cortisone. However, in the mouse, it has been demonstrated that subcutaneous administration of a large dose of cortisone does cause true myeloid hyperplasia (Quittner *et al.*[12]).

Another possibility is that the administration of corticosteroids may prolong the life span of the leukemic cell and thereby increase its effective period of action; however, there is no evidence for this. Although the mechanism remains obscure, there is now an increasing accumulation of clinical evidence that steroid hormones may aggravate certain cases of acute granulocytic leukemia. That this "steroid acceleration" phenomenon is the exception rather than the rule is indicated by numerous reports of beneficial effects of steroids in patients with acute granulocytic leukemia, including our own case 2.

THERAPEUTIC CONSIDERATIONS. It

would appear, then, that in acute granulocytic leukemia in pregnancy, a preference for therapy with corticosteroids rather than 6-mercaptopurine cannot be justified on grounds either of greater safety for the fetus or of greater likelihood of maternal benefit. Successful use of 6-mercaptopurine in this situation is exemplified by our case 4; others have reported the use of mercaptopurine in conjunction with cortisone (Merskey and Rigal[10], Schumacher[16]). In acute lymphoblastic leukemia, there is less basis on which to make a decision. If the patient were not acutely ill, a reasonable course might be to begin therapy with 6-mercaptopurine, and to reserve the steroids for emergency situations where rapid antileukemic action is needed, or for the rare patient in whom therapy is demanded in the first trimester, or for the patient whose leukemia is refractory to 6-mercaptopurine.

We believe that by virtue of its more fulminating character and more immediately fatal prognosis, acute leukemia provides a different problem in management from certain other hematologic neoplasms. In Hodgkin's disease (Smith, Sheehy and Rothberg[18]) and in chronic leukemia (Sheehy[17]) prognosis of the pregnancy is usually good; and because of the potential harmful effects of cytotoxic agents, their use should be avoided whenever possible. Where therapy is urgently needed, one should employ the minimum doses required to achieve the desired result; and in almost every such case, therapy can and should be deferred until after the first trimester. In acute leukemia, on the other hand, prognosis is poor, and few mothers can sustain a normal pregnancy. If a viable infant is desired, the only hope is to treat the leukemia vigorously with the aim of producing a remission or suppressing the disease for long enough to allow the pregnancy to reach term. At the present time, the agent most likely to achieve this end is probably 6-mercaptopurine.

Summary and Conclusions. Four cases of acute myeloblastic leukemia in pregnancy are presented, and the relevant literature is discussed.

The limited life expectancy of the patient with acute leukemia makes it highly unlikely that she can sustain a normal pregnancy. Fetal salvage is low irrespective of treatment. There is no evidence of transplacental transmission of leukemia.

Corticosteroid therapy may accelerate the course of acute myeloblastic leukemia.

In the management of acute leukemia in pregnancy, steroids are not necessarily superior to antimetabolites. The best overall therapeutic regimen is that which is most effective against the leukemia itself.

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SUMMARIO IN INTERLINGUA

Acute Leucemia Granulocytic In Pregnantia: Reporto De Quatro Casos, Con Acceleration Apparente Per Prednisona In Un

Es presentate quatro casos de acute leucemia myeloblastic in gravidas. Le pertinente litteratura es discutite.

Le restringite superviventia probabile del patiente con leucemia acute rende multo dubitose que illa pote completar un normal pregnantia. Le numero del fetos salvate es basse, sin reguardo a qual tractamento es usate. Il existe nulle indication pro le occurrentia de un transmission transplacental de leucemia.

Therapia corticosteroide pote accelerar le curso de acute leucemia myeloblastic.

In le tractamento de leucemia acute in gravidas, steroides non es necessarimente superior a antimetabolitos. Le melior regime therapeutic in tal casos es le regime que es le plus efficace contra le leucemia mesme.

ORAL PENICILLIN G AND PENICILLIN V

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The antibiotic blood level has seemed to assume great importance. In the initial investigation of a new antimicrobial agent pharmacologic study is required in order to make a preliminary estimate of its dosage. Although it is the concentration of the drug in the infected tissue that is of prime importance, antibiotic tissue levels are not easy to determine. Therefore, dosage requirements are usually based on combined information concerning the *in vitro* potency and blood level curves for given doses.

However, data on blood concentrations must be interpreted liberally with the cognizance of the tremendous range of biologic variability due to the operation of a host of uncontrollable factors. Even the so-called cross-over experiment results in mean data which must be viewed in the light of the standard deviation, for, the greater the variation in the figures the less applicable are the means to the treatment of the individual patient at the clinical level. Therefore, in the last analysis, it is the controlled study of comparative efficacy of a drug in human disease that counts. This concept is often lost sight of, or worse, ignored in these days of rapidly developing antimicrobial therapies with the result that the practicing physician may be misled into the use of allegedly advantageous new agents or chemical variants of older agents.

Those of us who are old enough to remember the developments which have occurred since the advent of sulfonamides can recall the rise and fall of the clinical importance ascribed to the blood level with each new drug as it appeared on the medical horizon. Furthermore, there have occurred from time to time seeming paradoxes which cast doubt on the clinical significance of antimicrobial blood concentrations in certain instances.

For example, penicillin dosage has been consistently predicated by most physicians on the concept that a more or less constant maintenance of this antibiotic in the human blood stream is essential to the success of treatment. This concept is erroneous, at least for infections due to penicillin susceptible organisms because excellent results have been achieved, in both animals and humans, with intermittent penicillin therapy. In 1948 and 1949 some clinical reports (Griffiths, Shooter and Heady[14], Southworth and Dobbs[35], Tompsett[39], Tompsett *et al.*[40], Weiss and Steinberg[44]) appeared which showed that penicillin susceptible infections respond to injections of crystalline aqueous penicillin at intervals of 12 to 24 hours despite the fact that

such dosage regimens result in demonstrable penicillemia for no longer than 4 to 8 hours (Tucker and Eagle[41]). Some of these clinical studies were uncontrolled by comparison to aqueous penicillin administered often enough to maintain constant penicillemia. Nevertheless, at the same time depot preparations of penicillin became popular for several reasons among which was the belief by the average physician that constant penicillemia is a *sine qua non* of therapy.

The same course of events might have occurred in the use of streptomycin in the treatment of tuberculosis if it were not for the fact that ototoxicity forced the recognition of the efficacy of intermittent regimens.

Other examples of the fallacy of basing dosage regimens exclusively on blood level curves might be cited but it is not necessary to belabor the point. It will suffice to emphasize the need for critical evaluation and healthy skepticism of claims which hint or frankly allege an advantage of certain forms of a drug over other forms simply because the blood concentrations are higher. One must ask: Are the blood levels high enough with the new form to have any clinical significance and, if so, then has a controlled study at the clinical level demonstrated definite superiority in the treatment of human infections? If these questions cannot be answered in the affirmative, then it is a disservice to our patients to prescribe the new form because it is usually more expensive.

It should be kept in mind that a majority of the common human infections which can be treated successfully with penicillin are due to organisms which are highly susceptible to this antibiotic; for example, pneumococcus, beta hemolytic streptococcus, gonococcus, and so forth. One need only recall the early days of penicillin therapy, when the usual dosage, due to scarcity of the drug, was 10,000 to 20,000 units intramuscularly every 3 hours, a total daily dosage of 80,000 to 160,000 units. Results were excellent and many lives were saved. It is doubtful that the results are any better today with the much larger doses used in common practice, except in certain uncommon diseases such as subacute bacterial endocarditis. Therefore, in everyday practice one questions the wisdom of attributing clinical significance to a mere doubling of the penicillin blood level. This applies to oral penicillin as well as to parenteral penicillin. It also may explain in part why probenecid achieved only temporary attention for the purpose of elevating blood concentrations of penicillin. Therapies which are based on inadequate appraisal cannot survive the test of experience.

Penicillin V has been presented as an improved form of oral penicillin for several years. A critical appraisal of penicillin V is in order. Arguments which favor the oral use of penicillin V over penicillin G are as follows: 1) blood levels of penicillin V are higher than those of penicillin G, and, 2) blood levels of penicillin V are not as greatly affected by the ingestion of food as is the case with penicillin G because penicillin V is acid-resistant. With these 2 premises a syllogism is usually constructed with the conclusion that penicillin V is more efficient than penicillin G, despite the fact that oral penicillin G was shown to be a highly effective dosage form for therapy of penicillin-susceptible infections (Denny, Wanamaker and Hahn[9], Flippin *et al.*[13]). We will now consider the validity of this syllogism.

It is true that the majority of pharmacologic reports on penicillin V corroborate the doubling of the penicillemia compared to that obtained with the

same dosage of penicillin G by mouth (Diding and Frisk[10], Elias and Merrion[11], Griffiths[16], Jones and Finland[20], Martin, Nichols and Heilman[24], Nichols, Jones and Finland[26], Putnam *et al.*[29], Rinsler and Cunliffe[31], Santos-Buch, Koenig and Rogers[32], Symon[38], Welch, Lewis and Staffa[45], Wright *et al.*[47]) but some reports (Cox *et al.*[7], Holborow, Bywaters and Johnson[17], Linden, Finegold and Hewitt[21], Peck and Griffith[27]) do not confirm this. In fact, Bunn[5] concluded that his data do *not* suggest that penicillin V can be prescribed in doses significantly less than the usual oral doses of penicillin G. Further, although the blood level of unbuffered penicillin G is diminished by prior ingestion of food, meals have no significant influence if the penicillin G is buffered (Jones and Finland[20]). In our own clinical experience the administration of adequate doses of this antibiotic (200,000 to 500,000 units 4 times a day) in the common penicillin-susceptible infections without respect to food intake has not lessened its efficacy.

Another argument in favor of penicillin V has been advanced by Spitzy and Hitzenberger[37] recently; when equal amounts of penicillin G and penicillin V are given *intravenously* blood levels of penicillin V are *lower* than those of penicillin G after diffusion equilibrium is established. This is interpreted to mean that more penicillin V passes into the tissues than penicillin G but these authors neglected to measure the renal excretion of these 2 antibiotics and therefore their interpretation is open to question.

Despite the higher blood levels obtained with oral penicillin V, a review of the available English literature uncovers certain other factors which would appear to nullify any clinical significance assigned *a priori* to the higher blood levels. *In vitro* the antimicrobial effect of penicillin V is generally of the same order of magnitude as that of penicillin G (Diding and Frisk[10]), although as much as 4 times the amount of penicillin G may be required for penicillin V to inhibit certain strains of bacteria (Jones and Finland[20]). *In vivo* the effect of penicillin V is the same as that of penicillin G in equal doses in eradicating streptococci from the throat (Wehrle, Feldman and Kuroda[42]).

Penicillin V is bound by plasma protein to a greater extent than is penicillin G (Anderson *et al.*[2], Smith, Levin and Embody[34]) and it is inactivated to a greater extent by guinea pig liver slices (Spitzy[36]).

Cuthbertson[8] has stated that penicillin G is more effective than penicillin V in the treatment of experimental staphylococcal and streptococcal infections in mice. Powell and Culbertson[28] indicate no differences in mouse survival rates (hemolytic streptococcus infections) with equal doses of penicillin G and penicillin V, even when the dosage is subeffective.

On the clinical level, there has been no proof that penicillin V is more effective than penicillin G when both are given by mouth in the same dosage. *All of the reports thus far are based on uncontrolled studies* (Alvarez-Pagan, Rees and Conway[1], Austrian and Winston[3], Breese and Disney[4], Finke[12], Mack and Christian[22], Martin, Nichols and Heilman[24], McWhorter *et al.*[25], Sheil[33], Wehrle *et al.*[43], Wood *et al.*[46]). This situation allows us to draw only inferences concerning the relative efficacy of these 2 penicillins by comparing the results in different series of cases, a comparison which often is not valid. Unfortunately, many investigators are content to publish uncontrolled studies and there is no other alternative for the reader but to compare different series.

For example, one report of the treatment of gonorrhea (Marmell and Prigot[23]) indicates that an oral dosage of 800,000 units of penicillin V failed to cure all of 5 cases and 1,200,000 units failed to cure 5 of 8 cases. In contrast, one expects to cure from 74% to 97% of patients with far less oral penicillin G in either single or divided doses (Bushby and Harkness[6], Jacoby, Pollock and Boghosian[18], Jacoby and Ollswang[19]).

The authors have treated 2 concurrent groups of young male adults suffering from acute pharyngitis associated with a beta hemolytic streptococcus in the throat secretions. One group of 25 patients received 200,000 units of penicillin G by mouth 4 times a day for 5 days while the other group of 26

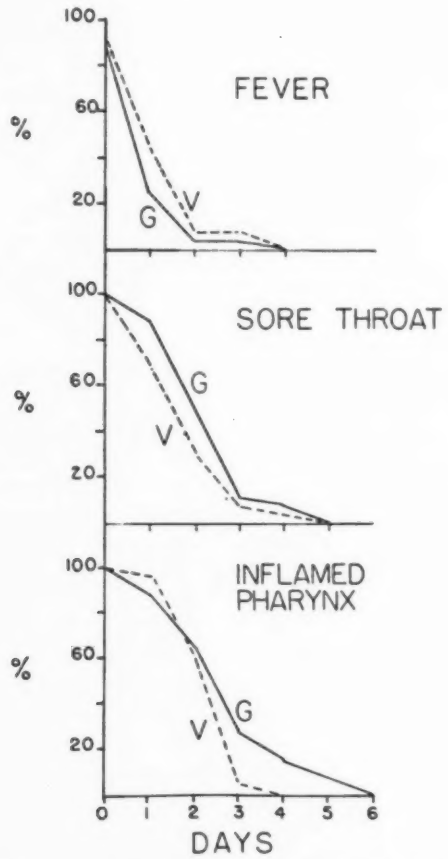

Fig. 1.—The percentage of patients with fever, sore throat and inflamed pharynx on each day after the start of treatment is plotted for 2 groups of young male adults. One group (G) of 25 patients was treated with 200,000 units of penicillin G by mouth 4 times a day for 5 days and the other group (V) of 26 patients was treated with the same dosage of pencillin V. There is no significant difference in the results. Several patients in the penicillin G group required a slightly longer period for resolution of inflamed pharynx than did patients in the penicillin V group because there were more severely ill patients in the G group than in the V group.

patients received the same dosage of penicillin V.* These 2 groups were comparable in every way except that there were 5 severely ill patients in the group treated with penicillin G and only 2 severely ill patients in the group treated with penicillin V. The observer was unaware of what medication each patient received.

The results are shown in Fig. 1. The percentage of patients in each group with fever, sore throat (subjective) and inflamed pharynx (objective) is plotted against time in days from the start of therapy. It is quite obvious that there is no significant difference between the group treated with penicillin G and the group treated with penicillin V. The slight discrepancy to be noted at the end of the curves for inflamed pharynx is due to the fact that there were more severely ill patients treated with penicillin G than with penicillin V and the resolution of pharyngeal inflammation required a longer period of time in the severely ill patients than in those whose illness was mild or moderate.

From the above remarks, it might be generalized that for penicillin-susceptible infections penicillin G is so good that penicillin V could do no more and might even do less.

In the case of infections which require high penicillin dosage such as subacute bacterial endocarditis (S.B.E.), a few cases have been treated successfully with oral penicillin V with or without probenecid (Cox *et al.*[7], Quinn *et al.*[30], Santos-Buch, Koenig and Rogers[32]). However, this must not be taken to mean that the same salutary effect could not be achieved with the same dosage of oral penicillin G with or without probenecid. In fact, Cox *et al.*[7] have reported a difference in average serum concentrations between large doses of penicillin V with probenecid compared to penicillin G with probenecid that is inconsequential from a clinical standpoint (8.5 compared to 7.5 gamma per ml. respectively). Most of the cases of S.B.E. treated with oral penicillin V have also received streptomycin so that it is not possible to draw any conclusions concerning the efficacy of penicillin V *per se*.

Summary. It has been assumed that higher blood levels and acid-resistance justify the conclusion that penicillin V is better than penicillin G for oral therapy. This rationalization is fallacious because: 1) oral penicillin G is effective therapy for penicillin-susceptible infections to the extent that penicillin V can do no better, 2) there is no controlled clinical evidence that penicillin V has any advantages over penicillin G, and, 3) penicillin V is no more effective and may be less effective than penicillin G in the treatment of infections of mice. Even for those who attribute clinical significance to the elevated blood levels of penicillin V, it should be noted that not all investigators are agreed that penicillin blood levels are significantly higher for V than for G, and the higher blood levels of penicillin V may be nullified by the facts that some strains of bacteria require more penicillin V than penicillin G for inhibition and that penicillin V is bound by plasma protein and inactivated by animal tissue to a greater extent than is penicillin G.

*The penicillins used in this study were potassium benzyl penicillin (Pentids, Squibb) and phenoxymethyl penicillin (V-cillin, Lilly).

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SUMMARIO IN INTERLINGUA

Penicillina G E Penicillina V In Therapia Oral

On ha credite que le plus alte nivellos resultante in le sanguine ab le administration oral de penicillina V insimul con le facto que penicillina V es resistente contra acido justifica le conclusion que le antibiotico in iste forma es melior que penicillina G pro le typo de therapia mentionate. Iste rationalisation es fallace proque (1) le administration oral de penicillina G es un therapia efficace in infectiones susceptibile al action de penicillina, in un tal grado que penicillina V non pote esser melior, (2) il existe nulle demonstration per tests a controlo que penicillina V ha ulle avantage in comparation con penicillina G, e (3) penicillina V non es plus efficace e possibilemente es minus efficace que penicillina G in le tractamento de infectiones in muses. Mesmo si on es preste a attribuer un signification clinic a elevate nivellos de penicillina in le sanguine, on non pote ignorar le facto que le investigatores non es omnes de accordo que le nivellos in le sanguine es plus alte in le caso de penicillina V que in le caso de penicillina G e que le plus alte nivellos de penicillina V, si illos existe, pote esser nullificate per le factos que certe racias de bacterios require pro lor inhibition plus penicillina V que penicillina G e que penicillina V es ligate per proteinas de plasma e es inactivate per histos animal a grados plus marcate que penicillina G.

THE PROBLEM OF BLOOD DONOR DISQUALIFICATIONS*

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and

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Every day the task of procuring the human blood wanted for transfusions in the nation's hospitals places a heavy responsibility on the established collection facilities. Besides age and weight barriers, thousands of persons are apathetic toward giving blood. Yet the diminution does not stop there; conservatively estimated, those who consider themselves physically able, and at the same time would be willing to respond if sufficiently urged, comprise less than one-fourth the general population of a typical region.

Women and first-time registrants constitute a decided minority of the individuals who do come to the collection facilities; consequently the separate respondents barely total 10% of the population. An even smaller proportion furnishes the therapeutic blood supply, owing to the numerous persons discovered to be medically unacceptable on presenting themselves to donate. Experience in Dade County, Florida, which includes Miami, shows that the disqualifications not only increase the difficulty of obtaining the requisite supply but also lay open to view several public health matters which are hardly disclosable from any other source.

SELECTIVITY. With emphasis on low hemoglobin levels, the succeeding paragraphs recount how the disqualifications vary between first-time registrants and repeaters, racially, and according to the ages of the individuals concerned. Material specially assembled at the John Elliott Blood Bank of Dade County enables essential comparisons to be made in reference to Caucasian men and women and Negro men (information adequate for one sex only) for the year October, 1956, to September, 1957, inclusive. Compositely the data relate to 22,675 persons, of whom 4,987, or 21.1% were not allowed to donate.

Consistent with a like differentiation earlier observed elsewhere (Hervey, Adashek and Gibson[3]), the physicians on duty during the blood collection operations rejected fewer persons who had given blood previously than those who were seeking to make initial donations (Table 1). Normal attrition partly accounts for the better record by the repeaters; subsequent to their last previous donations some persons reach the excludable age of 60 years, and physical impairments and deaths take a certain toll. Personal selectivity must also be recognized as being a potent factor (Boynton and Taylor[1]). Once turned down, many persons seem to develop a psychological resistance against ever trying again. Even individuals disqualified because of a common cold, poison ivy, or similar temporary ailment are prone to screen themselves from further attempting to give blood.

LOW HEMOGLOBIN LEVELS. Iron de-

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ficiency eliminated more persons as blood donors than did all other causes combined (Table 2). Though affecting the designated racial categories and the sexes unequally, almost 11% of the registrants became ineligible by failing to meet a routine test with copper sulfate solution (at specific gravity 1.055 for men and 1.053 for women). important as a single entity, and here the mean ages manifested inconsistent patterns.

As the proper medium for revealing how the incidence of subnormal hemoglobin changes through the entire age range, attention concentrates on the persons without prior donation experience. Those who volunteered to give

TABLE 1.—PERSONS PRESENTING THEMSELVES TO GIVE BLOOD FOR THE FIRST TIME COMPARED WITH THOSE WHO HAVE DONATED PREVIOUSLY, BY DESIGNATED RACIAL CATEGORIES

Category	*First-timers*	*Repeaters*	*Both classes*
Caucasian men:			
Total number	7,538	9,942	17,480
Number disqualified	1,740	1,260	3,000
Percentage disqualified	23.1	12.7	17.2
Negro men:			
Total number	1,460	1,570	3,030
Number disqualified	615	441	1,056
Percentage disqualified	42.1	28.1	34.9
Caucasian women:			
Total number	1,206	959	2,165
Number disqualified	493	238	731
Percentage disqualified	40.9	24.8	33.8
All categories:			
Total number	10,204	12,471	22,675
Number disqualified	2,848	1,939	4,787
Percentage disqualified	27.9	16.0	21.1

The Caucasian men were rejected in about one-third the relative frequency recorded for either the Negro men or Caucasian women. In general the men adjudged unsatisfactory were 2 to 4 years older than those found to be acceptable; and for the Caucasian women no similar difference in the average ages† could be detected. Of the causes unconnected with subnormal hemoglobin, 40 in all, none recurred often enough to be numerically blood for the first time during the year were unaffected by the attrition described for the repeaters. As a class, though, the initial registrants came from population strata above average in apparent health. Such distinctiveness affects the relations which Table 3 brings into objective view; the rejection percentages therein are believed to be lower throughout than those that would have been forthcoming had less restricted sampling been feasible.

†Average ages:

All Caucasian men: 35.2 years; those with hemoglobin subnormal, 38.9 years; hemoglobin satisfactory, 34.9 years.

All Negro men: 31.9 years; hemoglobin subnormal, 33.6 years; hemoglobin satisfactory, 31.4 years.

All Caucasian women: 38.0 years, with the difference between the above 2 elements not significant.

TABLE 2.—DISQUALIFICATIONS FOR LOW HEMOGLOBIN LEVELS COMPARED WITH THOSE FOR OTHER CAUSES, BY DESIGNATED RACIAL CATEGORIES

Category	*Low hemoglobin levels*	*Other causes*	*All causes*
Caucasian men (17,480):			
Number disqualified	1,268	1,732	3,000
Percentage disqualified	7.3	9.9	17.2
Negro men (3,030):			
Number disqualified	711	246	731
Percentage disqualified	23.5	11.4	34.9
Caucasian women (2,165):			
Number disqualified	485	246	731
Percentage disqualified	22.4	11.4	33.8
All categories (22,675):			
Number disqualified	2,464	2,323	4,787
Percentage disqualified	10.9	10.2	21.1

TABLE 3.—FIRST-TIMERS: DISQUALIFICATIONS FOR LOW HEMOGLOBIN LEVELS SHOWN IN RELATION TO AVERAGE AGE

(Individuals arranged into eight groups according to increasing age)

Group	*Average age, years*	*Number of Individuals*		*Percentage Disqualified*	
		Total	*Disqualified*	*Actual*	*Smoothed*
		CAUCASIAN MEN			
I	19.8	942	27	2.87	2.88
II	22.5	942	42	4.46	3.94
III	25.8	942	51	5.41	5.50
IV	28.9	943	64	6.79	7.26
V	32.8	943	91	9.65	9.22
VI	37.2	942	101	10.72	11.17
VII	42.0	942	116	12.31	12.70
VIII	51.1	942	140	14.86	14.41
All groups	32.5	7,538	632	8.38	8.38
		NEGRO MEN			
I	20.6	182	32	17.58	15.97
II	22.5	183	31	16.94	17.65
III	23.1	182	32	17.58	18.22
IV	27.5	183	41	22.40	22.67
V	29.7	182	46	25.27	25.01
VI	32.9	183	52	28.42	28.35
VII	38.7	182	67	36.81	33.63
VIII	48.4	183	66	36.07	39.56
All groups	30.4	1,460	367	25.13	25.13
		CAUCASIAN WOMEN			
I	21.3	151	31	20.53	22.34
II	24.8	151	36	23.84	23.90
III	29.7	151	40	26.49	25.34
IV	33.5	150	40	26.67	25.93
V	37.5	150	37	24.67	26.13
VI	41.1	151	40	26.49	25.44
VII	45.6	151	38	25.17	25.27
VIII	52.5	151	36	23.84	23.39
All groups	35.8	1,206	298	24.71	24.71

AGE RELATIONS. Evidently the male percentages proceed upward with ascending age. However, the absolute rise over one portion of the range differs from that over another. Examination of data from several extraneous sources widely dispersed in geographic origin persuades the authors on mathematical grounds that representation of the discernible trend as an arc tan function of age offers practical advantages for smoothing out the minor irregularities noticeable in the percentages as determined. This procedure gives an improved basis for securing impressions concerning the variability existent in the portions of the Dade County population from which the Caucasian and Negro men were drawn as prospective blood donors.

When the appropriate expressions are used for calculating the percentages in both male categories* the increases are seen to accelerate up to the age of 29 years and thereafter to continue rising but at declining rates. Data from other regions, reviewed as background for this report, indicate more generally that the transition point itself eventually may be established as a variant, occurring sooner or later than 29 years, depending on geographic location; a difference between the races does not seem to be likely. Physiologists will perceive that the smoothed values in each instance bear a partial statistical analogy to a segment of a sigmoid, organic growth curve (Pearl and Reed[5], Robertson[6]).

In regard to the contrasting subnormal hemoglobin situation ascertained for the Caucasian women, the fact that the physicians were compelled to disqualify nearly 36% of the first-time registrants made the percentages differ between the younger and older individuals within much narrower bounds than would have been witnessed under a lower average condition. Notwithstanding the constriction, the characteristic "horseshoe-type" variation, normally found in mass data on women, emerged. Calculations applied to the bottom section of Table 3, last column†, portray the disqualifications as increasing in relative frequency from a minimum for the women 18 years old (20.4%), staying above 25% from 30 to 46 years of age, and then dropping to 20.5% at 59 years. The actual maximum (26.1%), a barely perceptible turning point, came at 37.5 years.

ENVIRONMENTAL INFLUENCES. Although the correlations between subnormal hemoglobin and the factor of age prove to be so empirically measurable for both sexes, the multiform nature of the material studied warrants mention of only a few explanatory details, in part conjectural. "It is not surprising to find that iron deficiency anemia is more prevalent in the child-bearing female group. The excessive iron demands and iron loss of the female (menstruation, pregnancy, and lactation) can only be equalled in the male group by marked pathological blood loss. . . . It would also seem quite evident that this type of anemia would be more common in the lower economic group as a whole and in the groups with poor dietary habits"

*For Caucasian men:

$$\text{Disq.}\,\% = 7.208 + .119 \arctan(.080\,\text{age} - 2.320)$$

For Negro men:

$$\text{Disq.}\,\% = 24.627 + .310 \arctan(.060\,\text{age} - 1.740)$$

These expressions, which were derived by a process of approximation (Carmichael[2]), have standard errors of .39 and 1.80 respectively.

†For Caucasian women:

$$\text{Disq.}\,\% = 5\,\text{age} - 2.010\,(\text{age} + 1)^{1.2} - .770$$

Standard error = 1.04

(Kirschenfeld and Tew[4]). We know that in Miami and its environs persons who feel themselves socially and occupationally secure have a greater chance of acceptance as blood donors than persons less well adjusted. Moreover the identities of the registrants lend credibility to the thesis that station in life and the iron content of the blood are associated in some way not yet definable in precise objective terms.

On large groups of men influences which are possibly dietary find tangible manifestation in the changed incidence of iron deficiency between seasons (Hervey, Adashek and Gibson[3]). Between the 8 months October through May and the 4 summer months June to September, inclusive, the rejections of Caucasian males increased from 6.9% to 7.8%, and Negro males from 20.8% to 26.3%. A difference for the Caucasian females was too small to be significant. (This result should set at rest any opinion that an apparent seasonal variation must be attributed exclusively to an altered specific gravity of the copper sulfate solution, induced by the covers being off containers too long on warm days. Of course both sexes would have been affected if that contention had held true in the present case.) With respect to the non-hemoglobin criteria, fewer Caucasian men met the requirements in the winter than in summer; and the 2 other categories showed no seasonal change.

According to the U.S. Bureau of the Census estimates for the year 1955, 462,300 people reside in Dade County. Our calculations place the number of potential blood donors at 92,500, which figure far exceeds the present realized panel. Of these, 19,500 would be unacceptable on presenting themselves, including 10,100 for low hemoglobin levels. To a greater or less extent a similar situation prevails in the United States as a whole. Thousands of people learn about their iron deficiency when they undergo physical examinations or seek to donate blood. As a means of bringing home the facts to the additional thousands who are affected, the material on file in the numerous collection facilities should offer a fine opportunity for study.

Summary. Records on 22,675 persons who presented themselves to donate blood at the John Elliott Blood Bank of Dade County, Miami, Florida, in the year October, 1956, through September, 1957, show that 21.1% were medically unacceptable. Disqualifications for low hemoglobin levels (10.9%) exceeded all other causes combined. Hemoglobin deficiency among the Caucasian men in the sample occurred in approximately one-third the relative frequency determined for either the Caucasian women or Negro men. (No data are presented for Negro women.)

With respect to both male categories the hemoglobin disqualification percentages proceeded upward with increasing age to 29 years and then continued to rise but at declining rates to the excludable blood donor age of 60 years; this tendency was illustratively demonstrated for the men who presented themselves to donate blood for the first time. The corresponding percentages for Caucasian women tended to vary within comparatively narrow limits; nevertheless, the disqualifications were relatively more numerous between 30 and 46 years than at older and younger ages.

Disqualifications of the men for low hemoglobin levels were relatively more numerous in the summer months, this tendency being quite pronounced for Negroes. In all categories the disqualifications of individuals who had given blood previously were relatively fewer than those of the first-timers, owing to the factors of attrition and self-screening.

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SUMMARIO IN INTERLINGUA

Le Problema Del Disqualification De Donatores De Sanguine

Le dossiers de 22.675 personas qui se presentava preste a facer donationes de sanguine al Banca de Sanguine John Elliott del Contato Dade (Miami, Florida) durante le anno ab octobre 1956 a septembre 1957 monstra que 21,1% esseva inacceptabile ab le puncto de vista medical. Disqualificationes a causa de basse nivellos de hemoglobina (10,9%) excedeva omne le altere rationes combinate.

Carentia de hemoglobina in masculos de racia blanc in le presente studio occurreva con un frequentia relative de circa un tertio de illo determinate pro femininas de racia blanc o masculos de racia negre. Nulle datas es presentate pro femininas de racia negre.)

In ambe categorias mascule, le procentage del disqualificationes a causa de basse nivellos de hemoglobina cresceva con le etate usque al etate de 29 annos. Postea illo continuava crescer, sed nunc con un intensitate decrescente, usque al etate maximal pro donatores de sanguine que es fixate a 60 annos. Iste tendentia esseva demonstrate, como illustration, pro le masculos qui se presentava al donation de sanguine pro le prime vice. Le correspondente procentages pro femininas de racia blanc tendeva a variar intra comparativmente stricte limites. Nonobstante, le disqualificationes esseva relativemente plus frequente e etates de inter 30 e 46 annos que a etates plus avantiate e plus juvene.

Le disqualification de masculos a causa de basse nivellos de hemoglobina esseva relativemente plus frequente durante le menses de estate. Iste tendentia esseva specialmente pronunciate in subjectos de racia negre. In omne le categorias, le disqualification de subjectos qui jam habeca agite como donatores de sanguine esseva relativemente minus frequente que illo de subjectos de presentation initial. Isto se explica per le factores del attrition e del auto-selection.

NONSPECIFICITY IN BLOOD TRANSFUSIONS

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Biologists and members of the medical profession, especially hematologists, are well aware that under certain conditions Group O blood may be administered to individuals of other groups without serious consequences and with good therapeutic results (Strumia and McGraw[6]); A or B patients sometimes receive this "universal group" in emergencies and when the character of the immediately available blood supply so compels. We know, too, that some physicians feel justified to use A or B blood for AB patients (Mollison[4]). Furthermore, transfusion practices occasionally warrent deviation from specificity when employing low titer O blood in the treatment of ABO erythroblastosis fetalis. These considerations are predicated on efficient laboratory practices and selection of blood that will assure maximum safety on usage.

On the other side of the picture are sundry innovations which to date seem to have escaped studied review. Even with transfusions viewed as commonplace, having reached an estimated total of 4,585,000 a year in continental United States (Joint Blood Council[3]), competent observers agree that in some localities and hospitals procedural exactitude still requires greater attention. Within the scope allowed by a review of illustrative mass data, the present article stresses the need for remedial action.

basic principles. Many patients who receive transfusions are now immunized to some blood factors as the result of earlier transfusions which antedated the battery of laboratory tests currently available. "Past use of Group O blood without crossmatching has created the erroneous belief in some quarters that transfusion represents an uncomplicated form of therapy, whereas in reality it presents many hazards; besides, at least 25% of O donors have such a high titer of anti A and anti B agglutinins as to produce hemolysis of the recipients' red cells, and the titer cannot be reduced in all instances" (Newhouser[5]).

We know in addition that indiscriminate use of O blood without crossmatching can cause susceptible Rh-Negative persons to be sensitized by Rh-Positive blood. However small the chance of the combination may be, danger also attaches to the receipt of that Rh-Negative blood which happens to be positive for the Hr factor by those Rh-Positive patients who are negative for the Hr. Of course numerous other factors may cause immunizations. To go into further details would necessitate entering into an extensive review of the genetic and physiological principles which form the groundwork for modern transfusion therapy. The ramifications posed by the groups other than ABO, by various subgroups and types, literally scores of possible group-

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and-type antigenic conditions, and atypical agglutinins are all treated in standard texts.

Considered generally, a group or type difference between a blood donor and the ultimate recipient can occur: (1) necessarily, for technical reasons; (2) unnecessarily, even if permissible on technical grounds; (3) through carelessness, failure to crossmatch, faulty records, or incorrect bottle labels; or (4) despite well designed precautionary measures, owing to human error at some point in the chain of distribution from donor to recipient. Experience demonstrates that comparatively few instances fall in the first category. Altogether, the closer the approach to complete specificity in practice, the more assiduously are the collection facilities, hospitals, and physicians jointly striving to prevent transfusion reactions.

Material. To evaluate the composite importance of the above principles under typical operational conditions requires that a large body of factual material be gathered in a uniform way. Data relating to 30,063 pints* of blood which were obtained in a single Midwestern region and transfused to an estimated 13,100 patients in 72 local hospitals during the 12-month period September, 1956, to August, 1957, inclusive, meet the qualifications. In every instance the original donor record on file in the collection facility was checked against the blood usage report furnished by the hospital, showing the ABO group and Rh type of each recipient. According to the facility's medical director, the group and type proportions of both the recipients and donors followed usual monthly and annual patterns, thereby avoiding the bias that would have been introduced by an unrepresentative selection in time. Owing to the unprecedented nature of the study and to several possibly provocative findings, we prefer that the region, the hospitals, and facility go unnamed. (These omissions do not necessarily leave the region open to the charge of uniqueness in the matters treated; other data which have been made available yield quite similar results.)

Results and Discussion. Frequently when discussing specificity one hears the assertion that hospitals are overzealous in requesting and using O blood. Judgment on how that charge would apply to the region under present consideration can be reached most correctly by an indirect analytical route. As the starting point, entered in Table 1 for each group are the volumes of blood supplied to the hospitals and the portions transfused and not transfused to patients of like group. Calculations addressed exclusively to A, B, and AB raise very little, if any, suspicion that the recorded aggregate departures from specificity (13.9 per 1,000 transfusions) arose from more than chance causes. Including O with the aforesaid groups, the nonspecific transfusions mount to 32 per 1,000. The imbalance develops from the fact that nearly 1 in every 19 points of O blood administered was received by a non-O patient, a ratio far out of line with the incidence of O in a characteristic regional population (Hervey, Diamond and Watson[2]).

The inference that the above imbalance reflects an inordinate manifested demand for O blood obviously can be tenable only in the circumstance that both Rh-Positive blood and Rh-Negative blood had been transfused excessively in conjunction with the O. In reference solely to the use of A, B, and AB blood of positive type (Table 2), the relatively few cases (2.1 per 1,000 transfusions) in which Rh-Negative patients were the recipients could well have occurred undesignedly. Including Group O, however, the average for all Rh-Positive blood administered to Rh-Negative patients increases to 4.4 pints per 1,000. In statistical language, the incompleteness of matching between donors' and re-

*As employed in this report the word "pint" refers to blood of 440 ml. volume, without A-C-D solution.

cipients' blood assumes a hypernormal status in the presence of O and normal status in its absence. Here the aggregate nonspecificity, though small in terms of the total volume of supplied and transfused, seems to be ascribable more to an undue preference for O than for the positive type conjoined to this particular group. Nowhere in the course of the study was it possible to conclude that the hospitals or physicians intentionally sought or used Rh-Positive blood in proportions beyond its natural incidence.

A similar comment would be inappropriate concerning the opposite pairing. Aside from the Hr factor previously mentioned, the numerous unknown relations between a donor's blood and a recipient's make incongruous the revelation that Rh-Positive patients received approximately 130 pints per 1,000 Rh-Negative pints transfused. The subordinate group ratios show that inequities prevailed throughout (Table 3). Homogeneity tests applied to the data fail to support an assumption that the disclosed condition might have happened fortuitously; the explanation logically traces to intentional, causal influences. On the evidence, the tendency to use Rh-Negative blood in disproportionate volume greatly exceeded the concomitant inequitable preference for Group O blood.

Not all the determined nonspecificity, of course, indicated potential incompatibility. To elaborate briefly thereon the simplest procedure is to exclude from the sample all Group O blood transfused and all blood transfused to

TABLE 1.—BLOOD OF EACH DESIGNATED GROUP SUPPLIED TO HOSPITALS AND PORTIONS THEREOF RECEIVED AND NOT RECEIVED BY PATIENTS OF LIKE GROUP

	Number of pints			
Group	*Supplied and Transfused*	*To patients of group designated*	*To patients of different group*	*Nonspecific per 1,000 transfused*
O	13,866	13,130	736	53.1
A	12,627	12,442	185	14.7
B	2,611	2,584	27	10.3
AB	959	945	14	14.6
Aggregate	30,063	29,101	962	32.0

TABLE 2.—BLOOD OF RH-POSITIVE TYPE SUPPLIED AND TRANSFUSED AND PORTIONS THEREOF RECEIVED AND NOT RECEIVED BY PATIENTS OF POSITIVE TYPE

	Number of pints			
*Type**	*Supplied and Transfused*	*To patients of positive type*	*To patients of negative type*	*Nonspecific per 1,000 transfused*
(O) Positive	11,481	11,399	82	7.1
(A) Positive	10,598	10,574	23	2.2
(B,AB) Positive	2,935	2,929	6	2.0
Aggregate	25,014	24,902	111	4.4

*Letters in parentheses identify the groups with which the respective elements of the 25,014 positive pints were associated. B and AB are combined into a single class because the positive pints received by negative patients were too few to warrant separate classes.

AB patients ("universal recipients"). Of the 16,063 pints remaining, 52, or 3.2 per 1,000 used, denote group differences between the individuals who gave the blood and those who received it. Employing the gross sample total of 30,063 pints as the divisor, the ratio falls to 1.7 per 1,000 (Table 4); or, equivalently speaking, the mismatching can be estimated as having subjected one patient per 1,350 to the risk of a hemolytic reaction under the restricted conditions specified. For the reason that the relevant data from so many hospitals would have abounded in subjective judgments, ruling out comparability, questions concerning the actual incidence of reactions were omitted from the inquiry. No fatalities were reported.

Several hospitals advised that the nonspecificity, whatever its character, developed under "unusual conditions." Suddenly realizing that the blood in refrigerators had reached, or was nearing, the end of a 21-day outdating period, to avoid waste the laboratory technicians courted danger by allowing the stocks on hand to be used. Such liberty ran contrary to the practice adopted by the nation's larger blood users who are particular to return outdated stocks to the distributors and to obtain fresh supplies.

Requests for blood by the hospitals ordinarily provided for the maximum volumes anticipated for medical and surgical needs. Sometimes, though, the staff physicians when evaluating the prospective demand did not refer to

TABLE 3.—BLOOD OF RH-NEGATIVE TYPE SUPPLIED AND PORTIONS THEREOF RECEIVED AND NOT RECEIVED BY PATIENTS OF NEGATIVE TYPE

	Number of pints			
*Type**	*Supplied and Transfused*	*To patients of negative type*	*To patients of positive type*	*Nonspecific per 1,000 transfused*
(O) Negative	2,385	2,095	290	121.6
(A) Negative	2,029	1,803	226	111.4
(B) Negative	447	388	89	186.6
(AB) Negative	158	108	50	316.5
Aggregate	5,049	4,394	655	129.8

*Letters in parentheses identify the groups with which the respective elements of the 5,049 negative pints were associated

TABLE 4.—BLOOD OF EACH DESIGNATED GROUP SUPPLIED TO HOSPITALS AND PORTIONS THEREOF RECEIVED BY PATIENTS OF INCOMPATIBLE GROUP

	Number of pints						
	Supplied and Transfused	*To patients of incompatible group*					*Incompatible per 1,000 transfused*
Group		*O*	*A*	*B*	*AB*	*Total*	
O	13,866	—	—	—	—	—	—
A	12,627	27	—	3	—	30	2.4
B	2,611	2	6	—	—	8	3.1
AB	959	0	0	14	—	14	14.6
Aggregate	30 063	29	6	17	—	52	1.7

the experience records maintained in the laboratories. Occasionally also the physicians, having no alternative, insisted that definite volumes be made available over a short period; and their orders were kept in force too long. Moreover, some technicians hesitated to inform the clinicians that blood held in reserve for certain patients was needed for other patients. These contingencies underscore the necessity of taking measures to prevent waste in the supply whenever the consigned blood cannot be promptly used for the purpose originally intended.

The disproportionate use of Rh-Negative blood grew out of conditions which usually did not exist during the regular workday. If the blood was crossmatched at all, collateral circumstances induced errors and resultant mislabeling. Predominantly the errors were confined to the night hours when other persons were substituting for the technicians normally on duty. Unquestionably a shortage of adequately trained personnel on 24-hour call had much to do with the imbalance, notably in the smaller hospitals.

Whether the nonspecificity revealed by the sample should be considered large or small is a matter of opinion. But there can be no disagreement that under favorable conditions a recipient's serum can act on a donor's red cells and lead to serious post-transfusion consequences; indeed, "some foreign antigens are introduced in 80% of transfusions although only 5% are now recognized clinically" (Crisp[1]). Can there be any doubt that in an event which involves the passage of blood from one human organism to another the most meticulous care should be taken?

Summary. This report deals with the subject of nonspecificity between blood donors and recipients, based on data pertaining to 30,063 pints of blood which were transfused to an estimated 13,100 patients. Covering the 12-month period September, 1956, through August, 1957, the sample contained 72 hospitals located in a certain Midwestern region. The authors insist that meticulous care should be taken to insure complete group and type matching between blood donors and recipients.

In the aggregate, 32 pints per 1,000 transfused were received by patients whose ABO groups differed from those of the persons who gave the blood. To some extent Group O blood was used disproportionately. This practice was greatly exceeded, however, by nonspecific transfusions of the Rh-Negative; approximately 130 pints per 1,000 of such blood were received by Rh-Positive patients. Circumstances connected with the crossmatching induced errors and resultant mislabeling. Predominantly the errors were confined to the night hours when the regular technicians were off duty.

Excluding from consideration all Group O blood and blood received by AB patients, 3.2 pints per 1,000 transfused denote group differences between donors and recipients, or 1.7 per 1,000 total pints transfused. This last ratio indicates the chance of exposure to a hemolytic reaction under the restricted conditions delineated.

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SUMMARIO IN INTERLINGUA

Nonspecificitate In Transfusiones De Sanguine

Le presente reporto concerne le thema del nonspecificitate inter donatores e recipientes de sanguine, basate super datos pertinente a 30.063 pintas de de sanguine que esseva transfusionate a un total estimate de 12.100 patientes. Le periodo in question esseva le 12 menses ab septembre 1956 a augusto 1957. Esseva includite 72 hospitales in un certe area medio-occidental del Statos Unite. Le autores insiste que le plus meticulose attention debe esser prestate al complete appareamento per gruppo e typo inter donator e recipiente de sanguine.

In le total hic studiate, 32 ex omne 1.000 pintas de sanguine transfusionate esseva recipite per patientes de gruppo ABO differente del gruppo ABO del subjectos qui habeva donate le sanguine. In un certe mesura, le uso de sanguine del gruppo O esseva disproportionate. Sed iste practica esseva multo minus frequente que le transfusion nonspecific de sanguine Rh-negative. Circa 130 pintas ex omne 1.000 pintas de tal sanguine esseva recipite per patientes Rh-positive. Circumstantias connectite con le practica del appareamento produceva errores e resultava in un etiquettage incorrecte. Le errores esseva restringite predominantemente al horas nocturne quando le technicos regular esseva foras de servicio.

Si nos exclude omne sanguine de gruppo O e omne sanguine recipite per patientes AB, alora 3,2 ex 1.000 pintas esseva usate pro recipientes de gruppos differente del gruppo del donatores. Calculate pro le total de 30.063 pintas, le proportion es 1,7 ex omne 1.000 pintas. Iste valor de 1,7 pro mille indica le risco del exposition a reactiones hemolytic sub le restringite conditiones del presente reporto.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

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CARCINOIDS, THE MALIGNANT CARCINOID SYNDROME AND 5-HYDROXYTRYPTAMINE (SEROTONIN)

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HISTORICAL ASPECTS. Seventy years have now elapsed since the original acceptable description of a carcinoid tumor by Lubarsch[45]. This investigator's essay concerning multiple, small, whitish nodules in the submucosa and muscularis of the ileum leaves no doubt that the tumors to which he referred were carcinoids. He described the microscopic appearance of nests and strands of epithelial cells which did not resemble those of ordinary adenocarcinoma of the gastrointestinal tract and presented excellent illustrations.

It remained for Oberndorfer[53] in 1907 to coin the term "carcinoid." He felt that these tumors most likely were benign, although in 1890, Ransom[64] had reported a carcinoid tumor of the ileum with metastasis. Soon thereafter reports began to appear in increasing numbers describing and carefully documenting the behavior of the carcinoid tumor. With these data, it became increasingly apparent that the malignant potential of the carcinoid was much greater than had been anticipated in the early literature.

Beginning in 1930 there appeared six reports of the association of carcinoid tumors with metastatic spread and full blown pulmonary valvular stenosis. Cassidy[8,9] described this as-

sociation fully but failed to recognize the true significance of the pulmonary valve lesion. It was thought by most that the cardiac abnormality was either congenital or rheumatic in origin.

It was not until 1953, however, that the nature of the malignant carcinoid syndrome was revealed. At that time, three groups independently reported the existence of a true syndromal relationship (Thorson, Biorck, Walderstrom, and Bjorkman[83] in Sweden; Isler and Hedinger[40] in Switzerland; and Rosenbaum, Santer, and Claudon[68] in the United States). These investigators expressed the view that metastasis to the liver was an important factor in the genesis of this syndrome and that the common denominator in the production of its signs and symptoms was 5-hydroxytryptamine (serotonin).

INCIDENCE AND DISTRIBUTION. Carcinoid tumors are not common. The survey of combined surgical and necropsy cases in several large series[21,47,62,67] would indicate an incidence of 0.08% (138 carcinoids in 175,891 cases) with a range of 0.05% to 0.20%.

Carcinoids have been found in patients of almost all ages, from 10 days to 89 years. Those primary in the appendix are usually noted in the younger population, most cases having been observed in patients between ages 10 and 30 years. In contrast, primary tumors of other regions are usually found in older individuals averaging approximately 55 years of age. Acceptance of this discrepancy as being valid must be tempered by the fact that the vast majority of appendiceal carcinoids are associated with appendicitis which predominates in younger people. Whether the carcinoid is the cause of appendiceal obstruction and inflammation or whether its association is incidental in these cases is not known, although the former relationship appears likely.

While carcinoids are the most common primary tumors of the appendix, they may be found at any site in the gastrointestinal tract or its appendages. Numerous reports have indicated carcinoids of both benign and malignant nature in the stomach, the small intestine, the gallbladder, Meckel's diverticulum, the colon, ovarian teratomata, and more recently in the bronchial tree as a bronchial adenoma of carcinoid type. A review of the largest collections of these tumors[67] would indicate that approximately two-thirds of them arise in the appendix, about one-quarter in the jejunum or ileum, about 7% in the colon and rectum, about 2% in the stomach, and about 1% each in the duodenum, gallbladder, and other unusual sources. Of those arising in the jejuno-ileal area, the majority originate in the ileum.

MALIGNANT POTENTIAL. It was believed for a long time that carcinoids rarely, if ever, metastasize. More recent data, however, suggest that these tumors have a rather high malignant potential. The percentage of carcinoids which metastasize has been found to vary with the site of origin. Those most likely to spread are primary in the small intestine. While metastases have been found in almost every organ of the body, the most common sites of spread are the regional lymph nodes and the liver.

Dockerty[14] in 1955 stated that 75% of his series of carcinoids of the small bowel had metastasized. Recent reports indicate that approximately 50% of small intestinal carcinoids exhibit metastatic propensity. Of those lesions primary in the stomach, approximately 20% will spread. Approximately 50% of lesions of the colon and 8% of lesions of the rectum will extend beyond the site of origin. Metastases have also occurred from carcinoids primary in the gallbladder and Meckel's diverticulum.

Although rare, metastases from carcinoids of the appendix do occur.

It is apparent that carcinoid tumors must be accepted as malignant neoplasms and, although many have not metastasized upon discovery, no useful purpose is served by artificially separating them into benign and malignant forms, since there is no known method by which this distinction can be made accurately in the early stages of tumor growth.

Whereas the evidence indicates that a large number of carcinoid tumors manifest malignancy during the lifetime of the patient, few have presented the full blown picture described as the "malignant carcinoid syndrome." MacDonald[47], on the basis of 21 patients with proven liver or lung metastases from carcinoid primaries in the intestinal tract, noted that only four (19%) exhibited the carcinoid syndrome. Mattingly[50] estimated that clinically functioning tumors occur in as many as 25% of all malignant carcinoids of the small intestine. With the recent widespread publication of isolated cases or small series of cases, there has developed a better understanding of the clinical phenomena associated with the malignant carcinoid syndrome, and undoubtedly, many cases will appear in the literature within the next few years. Outstanding series include those of Thorson, Biorck, Bjorkman, and Walderstrom[83], Spain[78], Sjoerdsma, Weissbach, and Udenfriend[75], Daugherty *et al.*[13], McKusick[51], Hedinger and Gloor[30], Sauer, Dearing, and Flock[70], MacDonald[47], and others.

MULTIPLE SITES OF ORIGIN. The fact that carcinoids tend to be multiple in origin has been noted in several reports. Although it is conceivable that those with multiple tumors may result from a single primary, it would seem more reasonable, as in other endocrine disorders, that these tumors represent multiple primary sites. Marked variations in this tendency have been recorded, ranging from 16 to 34% of cases of extra-appendiceal carcinoid. Ritchie[67], in reviewing an extensive literature in 1956, found that 28% of the carcinoids primary in the small intestine were multiple, but that less than 10% of other extra appendicular carcinoids showed this tendency. As many as 68 primary carcinoid tumors have been recorded in one individual[80] and the experience of the author's institution includes a patient with forty tumors[63].

ASSOCIATED MALIGNANT TUMORS. In the series of carcinoid tumors reported in 1949 by Pearson and Fitzgerald[62], 9 of 29 tumors (31%) found at necropsy were associated with a malignant tumor of a different histologic type. In another series, Warren and Coyle[91] found that 10 of 19 asymptomatic carcinoids (53%) were associated with other malignant tumors. Foreman[23] noted associated malignancy of a different type in 7 of 15 cases of carcinoid tumors (47%). Although other reports have not been as striking, one must be aware of the occurrence of associated unrelated malignant lesions when evaluating a patient with a carcinoid.

PATHOLOGY. In the appendix, carcinoids vary in size from microscopic lesions to gross areas approaching 2 cm. in diameter, which in 75% of cases appear as enlargements of the tip. Smaller tumors may be discerned only on section of the appendix and are usually noted to be well-defined areas of firm, homogeneous, yellow or yellowish-gray tissue which has obliterated the distal portion of the lumen. These masses lie in the subepithelial fibrous tissue, and may or may not involve the muscularis. The overlying epithelium appears intact in some cases.

Extra-appendiceal carcinoid tumors characteristically appear as one or more

small, firm yellow or gray submucosal nodules, but occasionally they are polypoid, ulcerating or annular and constricting. The overlying epithelium is usually intact with the carcinoid movable beneath it. Miller and Herrmann[52] have suggested that as a result of the marked fibrous tissue hyperplasia associated with the tumor, the resultant kinking of the bowel might be employed as a diagnostic Roentgen sign of a carcinoid growth.

Microscopically, these tumors consist of nests, columns or masses of small, uniform, round, or polygonal epithelial cells lying in a fibrous stroma. Continuity between the epithelium of the overlying crypts and the tumor mass has been demonstrated. The clumps of tumor cells are usually solid without evidence of degeneration. The prominent nuclei are most often round with a well-defined nuclear membrane and abundant finely-stippled chromatin which is deeply basophilic. The cytoplasm is pale, indistinct, and acidophilic containing numerous acidophilic granules. The tumor cells are sometimes grouped around a space in such a manner as to simulate gland or rosette formation with the central space often containing an amorphous acidophilic material. Stout[81] has illustrated the "ribbon-like festoons" of tumor cells seen most often in rectal carcinoids. A single tumor may show more than one architectural pattern. The fibrous or hyaline connective tissue stroma is variable in amount, but is commonly prominent. A pseudo capsule is often formed by condensation of smooth muscle fibers at the periphery of the tumor. Mitoses are rare. However, pleomorphic tumors do occur with anaplastic cells, multi-nucleated cells, gigantic and bizarre nuclei and frequent mitoses. These anaplastic forms do not necessarily metastasize.

The granules, often present in the cells of carcinoid tumors, are likely artefacts produced by formal fixation. Unstained, the granules are yellow and react with many staining agents including iron hematoxylin, eosin, and acid fuchsin, Schmorl's ferric-ferricyanide, ammoniacal silver nitrate, ultraviolet light, and Gibbs-indophenol. The vacuoles of the cells stain with scarlet red, Sudan IV, and osmic acid. They show double refractile crystals when examined by polarized light. Mucin has been demonstrated by Meyer's mucicarmine stain. The exact nature of the granules is still under debate.

The limitations of silver stains in establishing the diagnosis of carcinoid tumor has been recognized. Failure to demonstrate granules which can be blackened by the Masson or Gomori method does not mean that a tumor is not a carcinoid, nor is a positive result unequivocal evidence that a tumor is a carcinoid, for other kinds of granules may give the argentaffin reaction. It should be emphasized that no histologic feature or features known enable one to distinguish those carcinoids likely to metastasize from those which will not.

PATHOGENESIS. Forbus[22] has provided an excellent account of the various theoretical explanations of carcinoid etiology. These included origin from pancreatic nests[1,53], from remnants of the omphalomesenteric duct[78], from heterotropic embyronic material[17], and from Auerbach's plexus[16]. Others have likened the carcinoid to basal cell carcinomata of the skin[7] to nevi[3] and to endothelial sarcomata[26]. Despite these multiple and varied opinions, the original proposal of Lubarsch that carcinoids were carcinomata arising from the crypts of Lieberkühn has survived and been strengthened. Additional support was provided by Huebschmann[38] in 1910, when he suggested that these tumors might arise

from either Paneth cells or Kultschitzky cells in the crypts of Lieberkühn, and by the outstanding work of Gosset and Masson[28] in 1914. The latter investigators showed that Kultschitzky cells contained granules which, under proper laboratory conditions, were acted upon by ammoniacal silver nitrate, and they demonstrated similar intracellular granules in carcinoid tumors of the appendix. Masson summarized this work by postulating that carcinoids originated from enterochrome chromaffin cells of the basi-granular layer of the crypts of Lieberkühn of the gastrointestinal tract. Pearse[61] has verified by histochemical means that the granules of carcinoid tumors are identical with those of the Kultschitzky cells, thus adding credence to Masson's work.

In man, the Kultschitzky cells (also called argentaffin cells) occur in the epithelium of the gastrointestinal tract from the cardia of the stomach to the anus, and in the epithelium of the biliary system and the major pancreatic ducts. They are particularly common in the crypts of Lieberkühn where they usually occur singly, lying between the other epithelial components.

No carcinoid has ever been found primary in a site in which Kultschitzky cells are not found. Finally, it has been shown that Kultschitzky cells secrete 5-hydroxytryptamine, a substance found in large quantities in carcinoid tumors.

SECRETORY ACTIVITY. Until the demonstration by Erspamer and Asero[18], in 1952, that the Kultschitzky cells secrete a substance identifiable as 5-hydroxytryptamine, many theories had been proposed concerning the secretory activity of these cells. Some thought them endocrine, some exocrine, some absorptive, some excretory.

Masson and Berger[49] insisted on the endocrine function of these cells and referred to the carcinoid tumors derived from them as endocrine tumors. Jacobson[41] proposed that they played some part in normal erythropoiesis, forming a substance necessary for the prevention of pernicious anemia. Weisberg and Schaefer[92], collecting a large series of carcinoid tumors from the literature, rejected the popular hypothesis that the Kultschitzky cells were similar to the alpha cells of the pancreas which secrete glucagon, the hyperglycemic-glycogenolytic factor. Others felt that histamine was the major secretion of the Kultschitzky cell, but this too was dispelled by Dockerty and Scheifley[15], Snow *et al.*[77], Waldenstrom and Ljungberg[90], and others. In 1936 a vasopressor substance was extracted from a carcinoid tumor, which was later shown to be different from adrenalin or acetylcholine.

At the time that Erspamer[18] was identifying his "enteramine" as 5-hydroxytryptamine, others were studying a substance called "serotonin." In 1949, Rapport[65] showed that serotonin was, in fact, 5-hydroxytryptamine. Barter and Pearse[4], and later Gomori[27], by histochemical techniques, added further support to the belief that Kultschitsky cells contained 5-hydroxytryptamine. Finally, Ratzenhofer and Lembeck[66] demonstrated that the reactions of the cells of carcinoid tumors were characteristic of 5-hydroxytryptamine.

Accordingly, it seems probable that the Kultschitzky cells secrete 5-hydroxytryptamine into the blood and some carcinoids share this function. It must be noted, however, that not all carcinoids produce this substance, and to this extent, Waldenstrom and Ljungberg[90] would appear to be correct in suggesting that carcinoid tumors may be of various types.

MALIGNANT CARCINOID SYNDROME. The essential features of this entity are a peculiar episodic flushing with telangiectasia of the skin, a curious macular cyanosis, chronic diarrhea, respiratory

distress and valvular disease of the heart, involving in order of descending severity, the pulmonary, tricuspid, mitral and aortic valves. These symptoms and findings are associated with a malignant carcinoid tumor which has metastasized, usually involving the liver.

The flush itself is often associated with a slight to marked fall in blood pressure. Thorson[82] has divided the flush into three stages. The first is characterized by reddening and burning beginning usually in the face and spreading over the trunk and extremities. The second begins when the flush and sensation of burning are fully developed, implying that cutaneous vasodilatation was complete, and is characterized by tachycardia with a rise in systolic blood pressure. The onset of the third stage is marked by pronounced cyanosis succeeding the reddening, and is followed, on occasion, by a marked rise in diastolic pressure with disappearance of the radial pulse. The changes disappear with regression of the cyanosis.

It has been stated that the episodes of flushing can be precipitated by the ingestion of alcoholic beverages and hot drinks and in addition, may be triggered by defecation, anxiety, anger, or by palpation of the enlarged liver or intra-abdominal tumor which these patients possess. There has been, however, a failure to demonstrate an increase of 5-hydroxytryptamine in the blood after ingestion of alcohol or food.

The diarrhea varies in severity with some patients having as many as 30 watery yellow to green foul movements in a single day. The diarrhea may persist during the night as well as during the day, and is rarely bloody.

The respiratory difficulties have taken the form of asthmatic attacks, usually of a minimal to moderately severe nature yielding easily to the usual medical measures.

MacDonald[47], in reviewing 57 cases of functioning carcinoid, reported 34 in which there were isolated, nonrheumatic lesions of the valves of the right side of the heart or in those patients with patent foramena ovale, combined lesions on the right and left side.

Schneckloth, Page, and Corcoran[71] found discrete renal function to be regularly depressed in patients exhibiting this syndrome, and Page[56] has suggested that arthritis may also be a component. In view of this, speculation has arisen as to the possibility that the malignant carcinoid syndrome is a form of "collagen disease."

DISEASES ASSOCIATED WITH CARCINOIDS. MacDonald[47] in his large series of cases, has mentioned the association of gastric and duodenal ulcers with metastatic carcinoids. In contrast to the incidence of 5.5% ulceration in 18,000 consecutive necropsies, ulcers were present in 38% of his patients. The significance of this association is not apparent at present.

PHYSIOLOGIC AND PHARMACOLOGIC PROPERTIES OF 5-HYDROXYTRYPTAMINE. A very extensive review by Page[56] has helped to clarify the present physiological status of 5-hydroxytryptamine. Because of intense interest in this substance, a voluminous literature has accumulated. It is obvious that this agent affects multiple organ systems and although in the description to follow, the effects are categorized, it should be emphasized that this is being done for the purpose of clarity. In reality, reactions of this substance *in vivo* occur simultaneously and involve widespread areas.

A. SOURCES OF SEROTONIN (5-HT). *1. Nervous System.* Twarog and Page[84], in 1953, noted the presence of 5-HT in the dog and rat brain. This was confirmed by others and its distribution

elaborated. The highest concentrations were found in tissues associated with the autonomic nervous system, and in the area postrema. Most of the 5-HT appears to be bound to mitochondria. The close association of the distribution of 5-HT and 5-HT decarboxylase in the brain stem, rhinencephalon and neostriatum has also helped to establish the concept of primary production in these areas. 5-HT has been detected in the spinal fluid of patients with head injuries, brain tumors, and meningitis.

2. *Platelets.* Of the blood elements, platelets appear to contain large amounts of 5-HT. Recent evidence would indicate, however, that they are not fully saturated with the substance. Hillarp, Hogbert, Nilson and Leo[35] have suggested that ATP is concerned with the binding and storing of biologically active amines in the adrenal medulla and in platelets. Zucker and Borrelli[95] found human platelets able to absorb very large amounts of serotonin, which helps to explain its high concentrations in the blood of patients with the carcinoid syndrome. They also have shown that serotonin does not form as a result of clotting, but rather is released from the platelets. Despite numerous studies in this field, the curious phenomenon of the storage and release of pharmacologically active agents by platelets has as yet received no logical explanation and remains in a relatively primitive stage.

3. *Mast Cells.* Benditt *et al.*[6] have demonstrated the presence of 5-HT in mast cells isolated from peritoneal washings of rats. Parratt and West[60] have confirmed and extended this work. Although mast cell tumors of mice contain large amounts of serotonin and histamine, dog mast cell tumors contain only histamine, and the latter is apparently true for humans.

4. *Gastrointestinal Tract.* Erspamer *et al.*[19] have measured the serotonin content of the gastrointestinal tract of many species, noting variations among them. The work of Dalgliesh, Toh, and Work[12] indicates that the mucosa of the intestinal tract contains the highest concentration of serotonin and the mucosa of the pyloric region of the stomach is the most productive area. This work strongly suggests the release of serotonin from the gastrointestinal tract.

5. *Lung.* Weissbach, Waalkes, and Udenfriend[93] found the serotonin content of lung very low in the guinea pig, but higher in the mouse, rat and rabbit. In addition, the enzymes which produce serotonin (decarboxylase) and destroy it (monamine oxidase), are also present in lung tissue, the latter in higher concentration. The work of Humphrey and Jaques[39] in demonstrating that an antigen-antibody reaction to rabbit platelets caused release of serotonin, and that of Herxheimer[32] showing the powerful broncho-constrictor action of serotonin have been largely responsible for stimulating studies concerning the presence of serotonin in lung tissue.

6. *Miscellaneous Sources.* The venum of the scorpion, the wasp, and the nettle contain large amounts of serotonin.

From this brief sketch, it is apparent that the distribution of serotonin is widespread in the body, large amounts being found in the brain, platelets, gastrointestinal tract, and spleen, and smaller amounts in liver, bone marrow, lung, thyroid, pancreas, and diaphragm.

B. IDENTIFICATION OF SEROTONIN. The measurement of plasma serotonin is far from being a standardized procedure. The release of serotonin from platelets is complex and all the factors that control it are not understood. This may in large measure, account for the difficulties in interpretation of plasma

levels. The method which seems to have the greatest potential usefulness is the spectrophotofluorometric method of Udenfriend, Weissbach, and Clark[87]. Special equipment is necessary in order to activate and measure emitted fluorescence in the 250 to 550 mu. range. Serotonin and other 5- hydroxyindoles are activated maximally at 295 mu. and emit fluorescent light which is maximal at 330 mu. As little as 0.05 μg. of serotonin is said to be measurable.

C. DETERMINATION OF THE METABOLIC PRODUCTS OF SEROTONIN IN THE URINE. The excretory product of serotonin is 5-hydroxyindole acetic acid. Udenfriend *et al.*[86] described the first useful methods for quantitatively determining 5-HIAA in urine. This has been invaluable in the diagnosis of the malignant carcinoid syndrome. The determination is based on the Gerngross reaction with 1-nitroso-2-naphthol. The administration of reserpine to patients with the malignant carcinoid syndrome causes a marked increase in 5-HIAA, and this serves as a useful method of diagnosis. Chlorpromazine administration to patients with malignant carcinoids causes a marked fall in urinary 5-HIAA excretion. The range of normal for 5-HIAA in the urine has been found to be 2 to 9 mg. per 24 hours. The recent reports that ingestion of bananas leads to increased excretion of 5-hydroxyindole acetic acid in monkeys and children suggests the advisability of careful questioning of the patient prior to collection of urine for determination of 5-HIAA.

D. METABOLISM OF SEROTONIN. The production of serotonin from 5-hydroxytryptophan was suggested by Udenfriend *et al.*[85], and a specific decarboxylase which catalyses the reaction of 5-hydroxytryptophan to serotonin and CO_2 has been found. This enzyme is widely distributed throughout the body, and is highly specific, operating at an optimal pH of 8.1. Employing C-14 labeled tryptophan, it was noted that this substance, in patients with malignant carcinoids, proved to be a precursor of serotonin and ultimately of 5-HIAA. Thus, the predominant pathway of tryptophan metabolism in patients with carcinoids seems to be through serotonin. Serotonin itself does not appear to cross the blood-brain barrier while 5-hydroxytryptophan does so.

Some investigators believe that serotonin is synthesized chiefly or entirely in the enterochromaffin cells and released from them, but the wide distribution of 5-hydroxytryptophan decarboxylase casts doubt upon this proposal. It is possible that these cells produce 5-hydroxytryptophan, which is then decarboxylated elsewhere in the body. Since serotonin does not appear to traverse the blood-brain barrier, there is good reason to believe that cerebral serotonin is formed within the nervous system itself. The presence of decarboxylase in sympathetic ganglia raises the question of a possible transmittor or inhibitor function of serotonin in transmission at neuronal synapses. Sjoerdsma *et al.*[74] conclude that oxidative deamination by monamine oxidase is the major metabolic pathway for destruction of serotonin.

As much as 60% of dietary tryptophan, ingested daily in amounts averaging 500 mg. is converted to urinary 5-hydroxyindoles in patients with malignant carcinoids according to Udenfriend, Weissbach and Sjoerdsma[88], while normally only about 1% is metabolized. They and others have suggested that the marked alteration in tryptophan metabolism results in concomitant disturbance in niacin metabolism and that this should be considered when thinking about pathogenesis. Smith *et al.*[76] found that the excretion

of 5-hydroxyindole acetic acid in patients with carcinoid was moderately effected by the level of tryptophan intake in the diet and also suggested that a restricted intake, combined with excessive requirements of the tumor might give rise to tryptophan or nicotinic acid deficiency. So far, no one has conclusively shown the clinical symptoms of niacin deficiency in patients with the carcinoid syndrome. Of special interest is the fact that in one patient with renal metastases, the urine contained serotonin in large amounts and 5-hydroxytryptophan as well. Udenfriend, Weissbach and Bogdanski[59] mention that carcinoid tissue synthesizes as much as 2 to 3 mg. of serotonin per gram of tissue.

Sjoerdsma *et al.*[73] have studied 19 patients with metastatic carcinoids and have pointed out that some patients with extensive metastatic deposits show neither all, nor even the most characteristic manifestations of the syndrome. A tracer study made in one patient with 5-hydroxytrytophan enabled them to calculate a tumor pool of 2.8 gm. of serotonin and a tumor mass of between 1 and 3 kg. A wide variety of stimuli seemed to induce attacks in their patients, the most convincing of which was the precipitation of the skin changes by pressing on a carcinoid tumor in the testicle.

E. CARDIOVASCULAR ACTIONS OF SEROTONIN. Page and McCubbin[57], on the basis of studies in anesthetized and unanesthetized dogs, concluded that serotonin injection elicits a sustained fall in blood pressure. They felt that the mechanisms responsible for this phenomenon include release of endogenous histamine by serotonin and the peripheral inhibition of neurogenic vasoconstriction. Hollander, Michelson, and Wilkins[36] found that single intravenous doses of serotonin in normotensive and hypertensive patients increased pulse rates, but had a variable, pressor-depressor or biphasic effect on arterial pressure.

MacCannon and Horvath[46], Page[56] and others have shown that serotonin administration produces a quick initial fall in cardiac output associated with the Bezold-Jarisch effect followed by a sharp moderately prolonged rise which closely paralleled the rise in arterial pressure. In addition both pulmonary and systemic vascular resistance increase.

The accumulated evidence seems to indicate that the response of the cardiac musculature to serotonin is variable and depends somewhat on the preparation used for the study. It increases the rate rather than the strength of contraction in the isolated papillary muscle preparation, whereas in the intact dog heart it increases the strength of contraction and slows the cardiac rate. When perfused through the anterior descending branch of the left coronary artery of dogs, it has been shown to create dilatation.

Comroe *et al.*[10] have reviewed the vasoconstrictor effects of serotonin on the pulmonary circulation. Even small doses of serotonin produced many-fold increases in pulmonary arterial pressure with a drop in mean systemic pressure and a rise in cardiac output. Although the pulmonary circulation is usually largely unresponsive to most substances affecting systemic vasculature, serotonin is an important exception. It appears to have a direct vasoconstrictor action on the pulmonary vessels, which largely accounts for the pulmonary hypertension. It has been suggested that serotonin is involved in the vascular effects of pulmonary embolism.

The chemoreceptor stimulating action of serotonin appears to vary with the dose of drug administered. It is a more powerful stimulant of the caro-

tid body chemo-receptors than is lobeline. However, local application of serotonin to the carotid sinus area provokes a reflex fall in arterial pressure, which seems to result from the local constriction action of the drug causing increased baroceptor stimulation. Heymans[34] in 1955 authoritatively reviewed the effects of various agents on the carotid sinus.

There remains no certain answer concerning the effects of serotonin on renal hemodynamics. Again the question of dosage is of paramount importance in defining the action of the drug. The possession of antidiuretic activity by serotonin is championed by Erspamer and Ottolenghi, and doubted by Corcoran *et al.*[11]. Recent studies in normal humans indicate that serotonin infusion reduces renal blood flow and glomerular filtration rate while causing a slight rise in mean pressure. It has been shown by several authors[31,55] that single intravenous injections of serotonin in lower animals produce visible blanching of the kidneys while prolonged infusion causes patchy areas of cortical necrosis. These lesions are suggestive of those noted in pregnant women who have died within 24 hours after the onset of severe abruptio placenta.

Serotonin effectively dilates the small foreleg vessels of the dog as well as the large arteries, while large veins may constrict. Since serotonin is able to elevate venous pressure, it appears likely that it influences water and salt distribution between intravascular and extravascular compartments.

Both intravenous and intra-arterial injections of serotonin cause a drop in blood flow to the skin of the arm. In addition, there is a decrease in forearm and hand blood flow with marked reddening of the skin changing to dusky blue in the fingers. This phenomenon is interpreted as demonstrating that serotonin constricts vessels concerned with peripheral resistance, but dilates the minute vessels of the skin.

Page and McCubbin[58,59] have shown that one of the most important factors in determining the vascular response to serotonin is the degree of neurogenic tone. Serotonin is a humoral antagonist to neurogenic vasomotor tone and so can provide the body with a chemical buffering system. Whether such a buffering system is actually used is not known.

The pressor action of serotonin may be augmented by cocaine, reserpine, Pituitrin, and bilateral nephrectomy. This pressor action may be reversed by abolishing the chemoreceptor activity of the carotid bodies, by injecting the drug into the portal vein and by simultaneously administering certain piperazine derivatives.

F. FEFECT OF SEROTONIN ON BLOOD COAGULATION. Although it was originally thought that serotonin reduced bleeding time, it is still not clear what function, if any, serotonin has in the coagulation mechanism. Platelet-serotonin content does not seem abnormal in a variety of diseases including pseudohemophilia, thrombocytosis and other blood dyscrasias. Platelet serotonin content tends to be reduced in patients with markedly elevated blood urea levels or with severe anemia. Serotonin added *in vitro* was found to be without effect on coagulation, clot retraction or fibrinolysis.

Kwaan, Lo, and McFadzean[42] showed that intravenous or paravenous injection of serotonin in human beings resulted in the development of fibrinolytic activity, not only in the plasma of the blood within the vein, but also within veins well removed proximally in the line of flow in the same arm and in veins in the opposite arm. This effect, abolished by reserpine, was felt

to be mediated through a cholinergic mechanism. Thus, it appears that a clot produced within a vein stimulates, through the serotonin release, fibrinolytic activity within the vein itself. In addition, it is felt by some that serotonin might be an antagonist of an antithrombin which blocks the reactions converting fibrinogen to fibrin.

Some evidence seems to indicate that serotonin increases capillary permeability, at least in part, by liberation of histamine.

G. ACTION OF SEROTONIN ON THE GASTROINTESTINAL TRACT. Although the exact mechanism of action is not completely clear, it is apparent that serotonin has a marked stimulating effect on various preparations of the intestinal tract used in experimental work. While some have drawn the provisional conclusion that serotonin acts upon the postganglionic cholinergic fibers of the intramural nervous system of the bowel, Gaddum[24] and Feldberg and Toh[21] feel that serotonin antagonizes the effect of acetylcholine. Levy and Michel-Ber[44] believe that this drug stimulates ganglion cells in the bowel to produce spasms. There appears to be an extremely high degree of sensitivity of several species to serotonin, suggesting that this drug might be important in the process of intestinal motility.

In addition, serotonin stimulates gastric acid production without effecting water secretion. Unlike histamine stimulation, this results in an increase in acidity without an increase in volume.

H. ACTION OF SEROTONIN ON BRONCHIAL MUSCULATURE. Serotonin is a potent bronchoconstrictor which could be the cause of many of the asthmatic attacks suffered by patients with malignant carcinoid tumors. Herxheimer[33] showed that guinea pigs forced to inhale an aerosol containing 1% serotonin developed bronchial spasm with severe dyspnea followed by convulsions. This syndrome is similar to that caused by anaphylaxis and histamine. Inhalation of serotonin aerosol in 4 normal human beings had no effect while in 3 of 6 asthmatics, it elicited severe asthmatic attacks. Aside from its respiratory effects mediated through the carotid sinus, serotonin apparently also effects vagal afferent fibers in lung tissue, resulting in rapid shallow breathing with eventual decline in spontaneous respiration.

I. ACTIONS OF SEROTONIN IN THE BRAIN AND ON MENTAL PROCESSES. While the exact mechanism of action of serotonin in the brain has not been defined, there is evidence to indicate that this substance is involved in mental function. The initial observation in this field was by Twarog and Page[84] who noted relatively large quantities of serotonin in the brain. Thereupon, Woolley and Shaw[94] showed that many antimetabolites of serotonin produced mental disturbances. Further impetus was provided by the finding of Gaddum[25] that LSD, a known hallucinogenic agent, is a powerful antagonist of serotonin. Brodie[72] added the fact that reserpine causes the liberation of cerebral serotonin and that this is associated with the tranquilizing effects of serotonin. In addition, Marrazzi and Hart[48] showed that serotonin depressed synaptic transmission within the brain causing mental disturbance. Finally, Udenfriend *et al.*[89] demonstrated that 5-hydroxytryptophan crosses the blood-brain barrier and is converted to serotonin in the brain. By protecting serotonin from destruction, behavioral changes resulted.

J. SEROTONIN ANTAGONISTS. While many compounds have been proposed as antagonists to the actions of serotonin, unfortunately none of the antagonists has been successful in the treat-

ment of patients with malignant carcinoids. The various substances included in this category are LSD, Bromo-LSD, Medmain (2-methyl-3-ethyl-5-dimethyl-aminoindole), Gramine derivatives such as 2-methyl-5-chlorogramine, a number of Dialkylindoles, antihistaminic agents, ergotamine, chlorpromazine, phenergan and diparcol.

TREATMENT OF CARCINOID TUMORS. The management of patients with carcinoid tumors presents several problems. There is no question that the treatment of choice is surgical excision. Benign carcinoids should be removed because they produce symptoms and because of their malignant potential. Malignant carcinoids should be resected whenever possible, together with as much of their metastatic spread as is feasible, since numerous reports in the literature demonstrate that even partial removal of these lesions results in prolongation of comfortable life for many years. By ordinary surgical standards, a metastatic nodule in the liver is a criterion of inoperability. However, when dealing with carcinoids, resection of the primary and metastatic lesion, even in the liver, appears justified. A note of caution must be interjected since there are a few reports suggesting that sudden release of serotonin has been responsible for death during the operative removal of carcinoid tumors even before any tumor tissue was manipulated.

There remains one area of the gastrointestinal tract where debate still exists as to the indications for radical surgical intervention. This is the rectal area where an increasingly larger number of carcinoid tumors have been identified. It is the present consensus of opinion[23,63] that a diameter of 2 cm. should be used as the dividing line between those carcinoids of the rectum which should be excised locally with an adequate margin of normal tissue and those tumors which should be subjected to an abdominoperineal resection. Other factors which might influence one in the direction of more radical intervention are annular or constricting lesions, tumors which appear fixed to the perirectal tissue and, of course, recurrent tumor masses in the rectal area. In contrast to the experience with small intestinal carcinoids, widespread metastasis from a rectal carcinoid is not compatible with long existence.

It has been hoped that some of the reported antagonists of serotonin would prove to be of value in the treatment of malignant carcinoid syndrome. As mentioned above, despite rigorous efforts, there is, at present, no adequate serotonin antagonist.

In patients who are not candidates for surgical therapy because of accompanying medical difficulties, one is forced to resort to symptomatic and palliative measures. Such agents as paregoric and Kaopectate have been effective at times in controlling diarrhea. In addition, the tranquilizing effect of chlorpromazine may have some value. If large amounts of histamine are being excreted in the urine, the administration of one of the antihistaminics may be of considerable value. Roentgen-ray and radioisotope therapy have been tried in an effort to destroy metastatic tissue and reduce amounts of circulating serotonin. Despite many attempts, no cures have been effected by these methods, although temporary palliation has been noted with the administration of radioactive gold.

Summary. An attempt has been made to define clearly the carcinoid tumor and the recently described malignant carcinoid syndrome. This tumor apparently functions in the same fashion as an endocrine tumor, secreting sero-

tonin. The physiology and pharmacology of serotonin have been elucidated. Treatment of this disease has been reviewed with emphasis on surgery and the potential value of serotonin antagonists. Prognosis is discussed.

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OPHTHALMOLOGY

UNDER THE CHARGE OF

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GLIOMAS OF THE OPTIC NERVE

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DESPITE, or perhaps because of, the relative rarity of primary intraneural tumors of the optic nerve and chiasm, a surprisingly large number of articles on the subject have been published recently. While some of these articles are essentially only reports of single or several cases, others present variant views on the microscopic pathology of these tumors, on their relationship to von Recklinghausen's neurofibromatosis and on the proper method of treatment. It is generally agreed now that all these neoplasms belong to the glioma family and, as noted by Dodge and his co-authors[20], the term "glioma of the optic nerve" has been employed commonly to designate a primary tumor arising in any part of the anterior visual pathways, the optic nerve, the chiasm or the optic tract. Clinically, lesions situated in different parts of the pathways present different symptoms and signs; but, histologically, they have the same characteristics.

LOCATION OF THE TUMORS WITHIN THE VISUAL PATHWAYS. Christensen and Ryan-Andersen[11] found that 6 of 12 verified gliomas involved the optic nerve only, while 5 involved the optic nerve and chiasm and 1 the chiasm only. Dodge and his co-workers[20] limited their study to tumors "primary in the optic apparatus from the emergence of its tracts from the optic globe to their entrance into the substance of the brain" and to cases in which positive surgical or necropsy material was available for study. These conditions were fulfilled in 46 cases seen at the Mayo Clinic between the years 1915 and 1955. The 46 cases were divided into 2 groups on the basis of the pathological findings. Group 1 comprised 12 cases in which the glioma was limited to one optic nerve. In the 34 cases in Group 2, the glioma was more diffuse and involved one optic nerve and the chiasm or the chiasm or the optic tracts, or both. A number of patients who appeared clinically to have a lesion limited to one optic nerve with unilateral loss of vision and proptosis were found at the time of exploration to have actually more diffuse involvement. Among 26 cases of intrinsic tumors of the optic nerve and chiasm reported by Walsh[77], there were 5 verified gliomas of the optic nerve and 14 gliomas of the chiasm, 12 verified and 2 not verified (1 of the latter was associated with generalized neurofibromatosis).

Wolff[79] stated that a glioma of the

optic nerve usually has its origin some 10 mm. behind the globe in the region of the entrance point of the central artery of the retina. From this point the tumor tends to grow towards the brain so that the part between it and the eye is apt to be free of new growth. Occasionally, however, the neoplasm has been observed to reach the papilla. In a Progress article in the Journal 3 years ago, I[75] stated, "A number of authors have noted that, though it is doubtful that a glioma ever has its site of origin in the optic disk, it is possible for a glioma of the intraorbital portion of the optic nerve to progress forward so that it is visible ophthalmoscopically." As instances of this I mentioned reports by Dandy[17], Davis[18], Hummelt[36], Verhoeff[74] and Wilson and Farmer[78]. Since that time Walsh[77] has mentioned the invasion of the optic disk by an astrocytoma of the optic nerve with a resultant ophthalmoscopically visible gray mass on the nasal side of the papilla. And Boles, Naugle and Samson[7] have reported a benign glioma of the optic nerve which apparently arose from the optic disk. It appeared ophthalmoscopically as a smooth, white, elevated mass at the upper margin of the disk and microscopically as a mushroom-shaped mass arising from the nerve head and projecting into the vitreous.

Grinker[29] thought that the point of origin of an optic nerve glioma was close to the optic foramen which becomes dilated early in the growth of the tumor. Contrary to the opinion of some observers, he thought that multiple foci of origin probably do not exist. Boles, Naugle and Samson[7] agreed that the vast majority of gliomata arise in the intraorbital portion of the optic nerve and that the commonest point of origin is in the region of the optic foramen. Growth can occur in both directions but usually towards the brain. Cushing[14] stated that gliomas arise from the chiasm or the adjacent wall of the third ventricle, whence they spread forward in some instances even as far as the retinal end of the optic nerve. One of the 7 cases reported by Martin and Cushing[55] had extended forward to involve the optic nerve head. Slade and Weekley[67] reported the case of an astrocytoma which they thought arose primarily in the optic tract. The details of this case are not too clear.

CLINICAL SYMPTOMS AND SIGNS OF GLIOMA OF THE INTRAORBITAL OPTIC NERVE. The basic symptoms and signs of a glioma confined to the intraorbital portion of the optic nerve are impairment of vision, proptosis and pallor or edema of the optic disk. Christensen and Ry-Andersen[11] described the clinical findings in somewhat greater detail. They noted that the impairment of vision is an early symptom and is rapidly progressive, that the protrusion of the globe is usually axial, non-pulsating and progressive, that restriction of movements of the globe is uncommon and that, though the tumor itself is rarely palpable, there is increased resistance to backward pressure of the globe. Ophthalmoscopic examination revealed atrophy of the optic disk in all of these authors' cases and papilledema in 1/3 of them; increasing hypermetropia was noted in some cases as a result of pressure by the tumor on the posterior surface of the globe. Braendstrup[8] thought that impairment of vision either preceded or developed simultaneously with proptosis, but Dodge and his co-authors[20] stated that, while 4 of their 12 patients were blind or had only light perception in one eye, 2 had 20/20 vision in each eye. Braendstrup[8] noted the folding of the retina associated with bulging forward of the posterior segment. Walsh[77] stated, "When 'ridging' of the retina

is an isolated finding involving the posterior pole of the eye, in our experience, it has usually meant that a mass is pressing into the posterior aspect of the eyeball, providing that the disc appearance is quite normal. If the disc is or has been swollen, ridging may be due to traction." Proptosis was present in all of the 12 cases reported by Dodge and his co-workers[20] and strabismus was frequent but due usually to unilateral blindness or impaired vision. Ophthalmoscopically, 7 of the 12 had unilateral papilledema on the affected side, 3 had pallor of the disk and 1 had a "pushed in" appearance of the posterior pole of the eye. The fundus of one eye could not be seen because of opacity of the lens. The ages of their patients ranged from 2 to 21 years and 10 of the 12 were females.

CLINICAL SIGNS AND SYMPTOMS OF GLIOMAS OF THE ANTERIOR INTRACRANIAL OPTIC PATHWAYS. As noted by Martin and Cushing[55], Cushing[14] and Braendstrup[8], the principal clinical evidences of gliomatous involvement of the intracranial portion of the optic nerve or of the chiasm are impaired vision, unilateral or bilateral, and optic atrophy, also unilateral or bilateral. Levitt[45] stated that a glioma which has its origin in the chiasm gives rise to rapid and progressive impairment of vision and bilateral optic atrophy. If fields are obtainable, there are apt to be hemianopic defects of very irregular character. Late in the course of the lesion, symptoms may develop which result from pressure on the third ventricle, hypophysis and hypothalamus—hydrocephalus, diabetes insipidus, lethargy, sleepiness, obesity and faulty sex development.

Dodge and his co-authors[20] placed 34 of their 46 cases in their second group, gliomas of the chiasm and optic tract. Loss of vision, usually bilateral and usually of bitemporal or incongruous homonymous hemianopic type, was the outstanding symptom and chief complaint. In 23 cases the impairment of vision was bilateral and in 9 of these it was typically bitemporal. In 8 cases the visual defect was unilateral and of prechiasmal type. Ophthalmoscopically, pallor of the disks of simple type was noted in 21 cases, in 17 bilaterally. Papilledema was found in 11 cases, unilateral in 5 and bilateral in 6. The vision and visual fields of one patient were normal in spite of the presence of bilateral papilledema of 4 diopters. Two patients were too young to be tested. Unilateral proptosis was present in 6 cases, 5 of which were clinically indistinguishable from cases with involvement of the optic nerve only. Strabismus of non-paralytic type was noted in patients with one blind eye. Three patients had searching nystagmus indicating that the onset of loss of vision had occurred early in life. The ages of the patients in this group ranged up to 46 years. There were 19 males and 15 females. Nine of the patients with intracranial involvement showed some endocrine disturbance such as precocious puberty, pituitary insufficiency, hypogonadism, eunuchoid habitus, obesity or mental retardation.

ROENTGENOLOGIC ASPECTS OF GLIOMAS OF THE OPTIC NERVE AND CHIASM. For the examination of the average case of suspected glioma of the optic nerve, routine roentgenograms of the skull with stereoscopic lateral views and special views of the optic foramens are sufficient. Enlargement of the optic foramen on the affected side, as judged especially by disparity in the size of the two foramens, indicates that tumor is present in the optic canal and is considered to be evidence that either a primarily intraorbital glioma is extending into the cranial cavity or that a primarily intracranial growth is in-

vading the orbital portion of the nerve. Decision as to whether an optic foramen is normal or not is sometimes difficult. According to Spaulding[68], an optic foramen over 6 mm. in diameter should be regarded as abnormal. Fowler and Matson[25] pointed out that the optic foramens are symmetrical in 45% of normal persons and that they differ in size as much as 10% in 40% and up to 20% in 15%. And it must be remembered that, as noted by Walsh[77] and by Rand, Irvine and Reeves[59], absence of enlargement of the foramen is not conclusive evidence that the tumor has not extended through it.

The sella is normal in cases in which the glioma is confined to the orbit and may be normal also in gliomas involving the chiasm and the intracranial portion of the optic nerve, particularly in the early stages. Martin and Cushing[55] described in 1923 a change in the sella turcica which they thought was characteristic of a glioma of the chiasm. They noted in 5 of their 7 cases "a recognizable anterior extension of the fossa which passes like the neck of a gourd under the anterior clinoid processes." This appeared to be due to pressure enlargement of the optic foramens. The gourd-shaped, pear-shaped or J-shaped sella has been noted by other observers, Fowler and Matson[25] and Levitt[45] for example. But this abnormality tends to be overlooked or regarded as congenital by some roentgenologists.

Other roentgenologic techniques which are valuable under certain conditions in the diagnosis of gliomas of the optic nerve are pneumoencephalograms, ventriculograms, carotid angiograms and orbital tomograms with or without air injection into the orbit. Grino and Billet[30] noted that cerebral angiography with 35% Diodrast permits radiologic visualization of orbital as well as intracranial tumors and is preferable to intraorbital air injection. They stated that astrocytomas of the optic nerve are poorly vascularized and will show a tumor shadow only very rarely but that angiographic diagnosis is made possible by displacement of the orbital vessels. Krayenbuhl[42] pointed out that the value of carotid angiography in the differential diagnosis of orbital lesions lies in the demonstration of the pathological vascularization of the space-occupying lesion rather than of the displacement of the ophthalmic artery and its branches. He[42] stated that the ophthalmic artery and its branches were demonstrated in 24% of 200 lateral carotid angiograms performed by the percutaneous technique with the injection of 35% Diodrast. With the use of a 60% contrast medium (Urografin-Schering), the ophthalmic artery was shown in 98% and the choroidal plexus of the eye in 74%. Krayenbuhl[42] had investigated also the possibilities of orbital phlebography by injection of contrast medium into the angular vein.

Routine roentgenograms of the head were negative in all 12 of the patients belonging to Group 1 of Dodge *et al.*[20]. Gross enlargement of the optic foramen on the affected side was present in 7 of the 8 patients who had rays of the optic foramens. Roentgenograms of the skull were normal in only 4 of the 34 cases in group 2. There were evidences of increased intracranial pressure in 6 cases. The region of the chiasmatic sulcus showed a large concave depression in 8 cases and a shallow depression in another 8. The authors[20] stated that this change is not pathognomonic but that, when combined with enlargement of one or both optic foramens, it should suggest the possibility of glioma of the chiasm. Pneumoencephalograms were made in 3 cases. All showed obliteration of the cisterna chiasmaticus and lamina ter-

minalis, posterior dislocation of the anterior portion of the third ventricle and an outline of part of the suprasellar tumor in the cisterna interpeduncularis, and also slight upward bulging of the floor of the anterior horn of each lateral ventricle. Ventriculograms were made in 4 cases and showed marked obstruction of the foramen of Monro in 3 and a lesser degree in 1. The lateral ventricles were dilated and there was upward convexity of the floors of the anterior horns. The two angiograms which were made were considered to be normal.

Spaulding[68] commented correctly that clinical diagnosis of glioma of the optic nerve is not always easy, especially in the early stages. In the cases in which specimens of the tumor were submitted to the Armed Forces Institute of Pathology, the period from the onset of symptoms to recognition of the nature of the lesion varied from 4 months to 2 years. An illustration of the difficulty in making the diagnosis of glioma of the optic nerve early in its development is given by Rucker[65]. A man, aged 36, complained of progressive deterioration of vision for 2 months. Vision of the right eye was reduced to the ability to count fingers. The right optic disk was elevated 6 diopters. The vision and fundus of the left eye were normal. The possibility of glioma of the optic nerve was considered, but the idea was discarded because the eye was not proptosed and its rotations were not limited. Fever therapy was administered for treatment of a presumed optic neuritis, but, within a few days, the eye became blind and the elevation of the optic disk had increased to 8 diopters. Two weeks later, right proptosis of 2 mm. became evident, upward and downward rotations of the right eye were limited and a paracentral scotoma developed in the visual field of the left eye. The right optic canal was not enlarged but right transfrontal craniotomy revealed that the right optic nerve was enlarged to 4 times its normal size by a swelling which extended backward through the chiasm into the right optic tract. Biopsy showed the lesion to be a malignant astrocytoma. Roentgen therapy was instituted.

DIFFERENTIAL DIAGNOSIS OF GLIOMA OF THE OPTIC NERVE AND CHIASM. Gramberg-Danielsen[28] listed some of the differential diagnostic features between glioma of the optic nerve and meningioma of the nerve sheath. In optic nerve glioma, most of the patients are less than 15 years of age, normal rotations of the globe are retained for a long time, the exophthalmos is direct forward, the optic disk is choked in the early stages and later becomes secondarily atrophic, vision is impaired before the onset of exophthalmos and progression is slow. In meningioma, most of the patients are over 20 years of age, ocular rotations are limited early, the exophthalmos is forward with displacement of the globe, the optic disk shows simple atrophy, vision is retained for a long time and progression is rapid.

Cushing[14] pointed out that gliomas of the optic chiasm might be distinguished from meningiomas of the tuberculum sellae by the following facts: they are largely restricted to childhood, the field defects are bitemporal in character but tend to be bizarre, the optic atrophy may be accompanied by a peculiar measurable elevation of the nerve head due apparently to the spread of the glioma down the length of the nerve and the sella is not expanded but has a pear-shaped or gourd-shaped forward expansion under the anterior clinoids due to pressure enlargement of the optic foramens.

Martin and Cushing[55] discussed the

differentiation of gliomas of the chiasm from craniopharyngiomas. A craniopharyngioma is characterized by primary optic atrophy on which edema may be superimposed later, bitemporal hemianopsia or, if one eye is blind, the retention of fairly acute vision in the seeing half of the other eye and by slow progression. The sella may be normal or may be variously deformed or enlarged. Suprasellar shadows are common. There are often secondary pituitary manifestations with adiposogenital dystrophy and infantilism. In the presence of a glioma of the chiasm, there is likewise primary optic atrophy on which edema may be superimposed later if the anterior part of the third ventricle is involved. Occasionally there is also gliomatous invasion of the nerve head. The bitemporal defects are less typical than those due to a craniopharyngioma and central visual acuity is low in both eyes. Progression is usually more rapid. The sella in an advanced case shows apparent forward extension under the anterior clinoids from distension of the optic foramens. There are no suprasellar shadows. Secondary pituitary manifestations are inconspicuous. Cutaneous lesions of von Recklinghausen's disease may be present if searched for.

PATHOLOGIC ASPECTS: GROSS AND MICROSCOPIC. To gross examination, an optic nerve glioma appears as a smooth-surfaced intradural enlargement of the nerve, fusiform, dumb-bell, spherical, spindle-shaped or diffuse, a solid irregular thickening along the entire course of the nerve. On cross section, there is visible the central rather solid subpial nerve stem and a surrounding more loosely textured mass filling the subdural and subarachnoid spaces.

Reese[60] states that the optic nerve has the structure, not of a peripheral nerve, but of a tract comparable to the intracerebral pathways of the white matter of the brain but differing in that it is subdivided into bundles delineated by vascular fibrous septa which enter from the pia. The nerve fibers composing these bundles are separated further by a glial network, the cells of which are of three types, astrocytes, oligodendrocytes and microglia. Special staining methods, such as Cajal's with gold chloride, del Rio Hortega's with silver carbonate, Weil-Davenport's with ammoniacal silver and others, are necessary to bring out the cytological details of these cells. The astrocytes have a large cell body from which there are cytoplasmic extensions or processes. The oligodendrocytes are recognized as rows of cells with small round nuclei. The microglia, which are probably of mesodermal origin and which do not participate in tumor formation, have small, oval or elongated nuclei from which short delicate expansions extend in all directions.

According to Liss and Wolter[46], Hudson[34] was the first to recognize the glial nature of intrinsic tumors of the optic nerve but he thought of them as instances of "gliomatosis" and not as true neoplasms. Hudson[34] published his observations first in 1912 and, apparently, he[35] held the same views in 1940, for he said then that "the tumours were manifestations of an overgrowth of neuroglia in tissues which had previously been exposed to some deleterious influence, and were therefore not true neoplasms, but manifestations of a degenerative gliomatosis."

On the basis of his studies of 11 specimens, Verhoeff[74] decided that the primary intraneural tumors of the optic nerve were gliomas: they were all composed primarily of neuroglia similar to the neuroglia of the normal nerve. He described 3 main types of tissue in the tumors: (1) finely reticulated with delicate glial fibers and small cytoplasmic vacuoles; (2) coarsely reticu-

lated with coarse fibers and large vacuoles giving a myxomatous appearance and with cystoid spaces; (3) coarsely fibrillated with spindle-shaped cells, resembling spindle-cell sarcoma. There was no evidence of direct or indirect division of cell nuclei, indicating a slow rate of cellular proliferation.

Verhoeff[74] stated that the tumor breaks through the pia and grows in the subdural space. Due to the mechanical distension of the subarachnoid space, a proliferation of the arachnoid tissue often takes place. It is unlikely that there is a stimulating factor elaborated in the glioma. The proliferated mass of arachnoidal cells may be invaded later by the cells of the glioma. The growth increases in size, not by invading or destroying the original nerve structure but by causing the preexisting neuroglia in the vicinity of the growth to proliferate. The cysts in the tumors are due to an extension of the process of cell vacuolization which is a characteristic of neuroglia cells. Verhoeff[74] thought that the cytoid bodies, which are quite frequent in these tumors, were atypical or giant neuroglia fibrils filled with a substance which stained like hyaline and which might be the residue of hemorrhage. Verhoeff[74] did not name any particular cell type as predominant or basic in the development of gliomas of the optic nerve. Neither did Martin and Cushing[55] in their 7 cases which they diagnosed microscopically as gliomas.

In 1942, Regoli[61] made a survey of 399 reported cases of tumors of the optic nerves. Among the 250 intraneural tumors, 124 had been diagnosed as gliomas, 108 as sarcomas and 18 as myxomas. Regoli[61] was inclined to think that all of these were actually gliomas. Most, if not all, recent writers classify all intraneural tumors of the optic nerve as gliomas and disagreement comes only in designating the cell type of the glioma. The cell types of the gliomas in their cases were not specified by McFarland and Eisenbeiss[56], Francois and Rabaey[26], Manschot[52], Berg[5], Donahue[22], Hanberry[31], Fowler and Matson[25], Jaensch[37] and Beuerman and Tabor[6]. Hanberry[31] stated that the tumor in his first case would have been considered by most observers to be a polar spongioblastoma and that in his second case an astrocytoma. Hanberry[31] commented that most authors seemed to think that gliomas of the optic nerve are either polar spongioblastomas or astrocytomas and that a few considered them to be oligodendrocytomas. He wrote: "Even though it is quite probable that many of the glial nuclei seen in areas of increased cellularity within the nerve stem represent oligodendrocytes, the neoplastic glial tissue which is growing in almost pure form in many areas of the invaded subdural space shows absolutely no resemblance to oligodendrogliomas observed within the cerebral hemispheres." The large astrocytes thought by Davis[18] to be the type cell of the gliomas are probably mere reactive astrocytes and not true neoplastic cells. Hanberry[31] added: "It would seem very likely that the vast majority of the previously reported gliomas of the optic nerve all belong to the astrocyte series, and that all probably contain both astrocytes and polar spongioblasts. . . . If all such cases contain these two types of glial cells in varying proportions, it is perhaps not worth while attempting to proceed further with classification, other than to designate such neoplasms as gliomas of the optic nerve." And Fowler and Matson[25] noted that, though there have been convincing reports of glioblastoma multiforme originating within the optic nerve, as a rule gliomas of the optic pathways are

more benign. They concluded: "Regardless of what the primary cell may be in this neoplastic process, the tumors seem to have a consistent histologic pattern and therefore they have been designated only as gliomas of the optic pathways rather than by a more specific histologic classification."

Saebo[66] classified the expansively growing and polymorphic tumor of the optic nerve which he removed incompletely from the orbit of his patient as a glioblastoma multiforme. There were numerous primitive cell-forms of gliomatous type. Besides the unipolar, bipolar and tripolar cells which resembled immature glial cells, spongioblasts and astroblasts respectively, there were multipolar cells with a better developed cytoplasmic pericaryon which resembled mature astroglia. Mitoses were frequent and occasionally incomplete. There were some multinucleated cells. The leptomeninges were infiltrated by lymphocytes and fibroblasts, but the dural sheath was free. Saebo[66] commented that, contrasting with the usual slow progression of gliomas, the progress of this tumor was rapid and death occurred 2 years after the onset from cerebral involvement.

In discussing the pathology of gliomas of the optic nerve, Grinker[29] noted that the pia-arachnoid and septums are often tremendously thickened so that the pia-arachnoid growth may be larger than the nerve tumor. This almost gives the impression that there are 2 tumors, one of the sheath structures and the other a glioma. This type of reaction is peculiar to the optic nerve. He stated that a couple of oligodendrogliomas had been reported, but "All the other tumors, however, seem to be definitely spongioblastomas (unipolare et bipolare). They follow typically the characteristic appearance of this type when found in the brain. The fusiform bipolar cells with delicate processes revealing frequent mitotic figures and hyaline degeneration are identical with bipolar spongioblasts. These tumors show frequent neoplastic giant cells, degenerative vascular changes and endothelial stimulation leading to vascular occlusions, cysts and hemorrhages. The malignancy of the tumor follows the fact well established by Bailey and Cushing[2] that the earlier the cell type in the histogenetic series, the more malignant is its nature. No differentiation of the spongioblasts into more adult glia in the tumors of the optic nerves has been found. Since astrocytes and oligodendroglia have been found in the normal optic nerve by Enriquez[24] and Marchesani[53], further developments should lead to the discovery of other tumors of the glia series arising from this nerve."

The gliomas of the optic nerves in their cases were designated spongioblastomas by Goldstein and Wexler[27], Rand, Irvine and Reeves[59], Wilson and Farmer[78], Bucy, Russell and Whitsell[9], Hummelt[36] and Gramberg-Danielsen[28] (Goldstein and Wexler[27] used the term, spongioneuroblastoma). Goldstein and Wexler[27] and Gramberg-Danielsen[28] pointed out that the spongioblast is the parent cell of the glia cells, both the astrocyte and the oligodendrocyte, which are the components of the neuroglia from which gliomas arise.

According to Reese[60], del Rio Hortega[62] thought in his early studies that the oligodendroglia of the optic nerve were comparable to the Schwann cells of the peripheral nerves in that they both have to do with supplying the myelin for the neurites. Reese[60] thinks that the occurrence, therefore, of medullated nerve fibers of the retina in patients with neurofibromatosis favors Hortega's[62] and Penfield's[58] conception that gliomas of the optic nerve are oligodendrocytomas. Later, in 1940, del Rio Hortega[63] said that the

denomination of these tumors might be either "longicellular astroblastoma" or "schwannoid oligodendrocytoma." Their cells, he thought, had no spongioblastic characters. Their degree of differentiation corresponded to that of the astroblasts and astrocytes, but morphologically they were more similar to schwannoid oligodendrocytes. In 1943, del Rio Hortega[64] stated, according to Liss and Wolter[46], that there were 3 types of glioma of the optic nerve, glioma longicellulare, oligodendroglioma and astroblastoma.

Lundberg[50] reported 9 cases of glioma of the optic nerve and chiasm as oligodendrogliomas, and Jain[38] reported a single case under the same designation. Braendstrup[8] described 2 primary tumors of the optic nerve as oligodendrocytomas. Christensen and Ry-Andersen[11] studied 12 gliomas of the optic nerve and chiasm. They observed 4 main types of cells: (1) a rather small cell with a round nucleus, a faintly staining cytoplasm, distinct cell outlines, and delicate fibrils forming a syncytium (resembling normal oligodendroglia cells in the brain); (2) a more coarsely reticular type of cell, oligodendrocyte, specific for this form of growth, of polygonal shape with a large, dark nucleus and fewer but coarser syncytial fibrils; (3) a sickle-shaped type of cell with coarse, short glial fibrils, which appears to be interpretable as an astrocyte; and (4) large cells resembling nerve cells or neuroblasts with one or more nuclei (present in some of the tumors). Christensen and Ry-Andersen[11] concluded that, histologically, gliomas of the optic nerve are benign and rather mature. The actual tumor cell, the oligodendrocyte, proves to be of glial origin, probably originating from oligodendroglia. It is spindle-shaped with an oval nucleus and slender, straight or tortuous fibrils building a syncytium.

In the specimen which they studied, Liss and Wolter[46] noted 3 types of cells: (1) elongated or spindle-formed, mostly bipolar Schwann elements; (2) round multipolar oligodendroglia and oligodendroblasts; and (3) astrocytes and astroblasts in small numbers. They thought that only the cells of type 1 and 2 were important to the classification of the tumor and that neither of them predominated as there were many cells of intermediate form. They concluded that the tumor should be classified as an oligodendroglioma since the two types of cells represented only different degrees of maturation and adaptation to different requirements. They pointed out that, in reproducing the normal activities of oligodendroglia, the oligodendroglioma of the optic nerve produces vast amounts of Schwann elements in different stages of maturation.

It is apparent that, since Davis[18] published his studies of gliomas of the optic nerve in 1940, many authors have agreed with his interpretation of the nature of these neoplasms. The 5 tumors reported on by Davis[18] were made up of both astrocytes and oligodendrocytes, but the astrocytes definitely predominated. Since normally the oligodendrocytes outnumber the astrocytes while in these tumors the number of astrocytes was enormously increased, the tumors were classified as astrocytes. Davis[18] recognized 5 stages in the development of optic nerve gliomas. In stage 1, there is generalized hyperplasia of the neuroglia within the nerve stem with proliferation of both astrocytes and oligodendrocytes and early fiber formation by fibrous astrocytes. In stage 2, there is progressive glial proliferation with extension of the growth through the pial sheath and hyperplasia of the arachnoid cells. In Stage 3, there is intermingling of the glial tumor with the proliferated arachnoidal cells so that landmarks are lost.

In stage 4, the gliomatous growth has destroyed most of the landmarks of the sheath including the growth in the arachnoidal sheath. The dura is invaded and partly destroyed by the growth. In stage 5, all landmarks within the nerve stem and sheath are completely obliterated. The cells are spindle-shaped and closely packed, resembling sarcoma cells. But differential stains show them to be astrocytes and oligodendrocytes.

Though they did not specify the cellular type of the optic nerve gliomas in their cases, Dresner and Montgomery[23] stated that the gliomas are commonly astrocytomas. Reese[60] apparently considers that gliomas of the optic nerve are astrocytomas. Walsh[77] stated in 1956 that most of the gliomas in his series were regarded as astrocytomas; 2 were thought to be oligodendrogliomas. Walsh[77] questioned the tenability of the diagnoses in 2 of his cases in which the tumors were said to be neurofibromas, one of the optic nerve and one of the chiasm. He suggested that they might have been oligodendrogliomas. In his 1947 text, he[76] had stated that gliomas of the optic nerve usually are either astrocytomas or spongioblastomas. Taveras, Mount and Wood[71] observed 34 patients with gliomas of the optic nerve or chiasm, or both. Nineteen were pathologically verified and all proved to be piloid astrocytomas. Later, Taveras[70] commented that almost all gliomas of the optic nerve and chiasm are composed of piloid astrocytes. Spaulding[68] stated that an optic nerve glioma may grow from any of the neuroglial cells, astrocytes, oligodendrocytes or microglia. The dominant cell is usually the astrocyte. But many specimens show an equal distribution of astrocytes and oligodendrocytes.

The gliomas in their cases were considered to be astrocytomas by Dandy[17], Love and Benedict[47], Horns[33], Rucker[65], Mann, Yates and Ainslie[51], Love and Dodge[48], Marshall[54], Craig and Dodge[12], Levitt[45], Love, Dodge and Bair[49], Slade and Weekley[67], Levatin[43], Hartemann, Dureux and Algan[32], Uihlein[72] and Uihlein and Rucker[73]. Dodge and his co-workers[20] divided their cases from the pathologic standpoint into 3 groups: Type A, tumors of the optic nerve, of which there were 12; Type B, tumors of the chiasm, of which there were 14; and Type C, "tractal" or diffuse tumors, of which there were 20. All 12 of the tumors of Type A were astrocytomas. Nine of the 12 were fibrous astrocytomas. Seven of the astrocytomas were graded 1, 4 were graded 2 and only 1 was considered to be an active neoplasm and graded 3. Thirteen of the 14 tumors of Type B were astrocytomas; 6 were graded 1, 5 were graded 2 and 2 were graded 3. One tumor was an oligodendroglioma, graded 3. All of the 20 tumors of Type C were astrocytomas; 15 were graded 1, predominantly fibrous in type, 4 were graded 2 and 1 was graded 3.

THE ASSOCIATION OF GLIOMAS OF THE OPTIC NERVE AND CHIASM WITH VON RECKLINGHAUSEN'S DISEASE. An abortive form of von Recklinghausen's neurofibromatosis was present in each of the 5 gliomas of the optic nerve reported by Davis[18] in 1940. Davis[18] was able to collect from the literature of the preceding 67 years 32 apparently authentic examples of this association. Cases reported by Cushing[14], by Martin and Cushing[55] and by Goldstein and Wexler[27] were included in this group. He[18] wrote: "The association of tumors of the optic nerve with Recklinghausen's disease can no longer be regarded as a coincidence. From the evidence now available, it appears that tumors of the optic nerve, especially of the glial type, are in many

instances but one manifestation of the disease. While they are more often associated with the abortive peripheral form of the disease, deep-seated lesions are likely to accompany them. It is a curious clinical fact that tumors of the optic nerve do not usually accompany the more typical variety of Recklinghausen's disease in which there is widespread tumor formation all over the body, though there are notable exceptions to this. No satisfactory explanation for this is known. . . . Since patients with tumors of the optic nerve associated with Recklinghausen's disease frequently show only the mildest general manifestations of the disease, such as café-au-lait pigment spots in the skin, it is important that ophthalmologists subject every patient, especially children, to a rigid search for these patches. They should be on the alert also for other general signs, such as deformities of the skeleton, particularly scoliosis."

Davis'[18] report stimulated interest in the possible relationship of optic nerve glioma to neurofibromatosis and a great deal has been written on the subject since 1940. And yet there is still no universal agreement on the actuality of the presumed relationship or on the percentage frequency of the association. Marshall's[54] statements may help to explain some of these differences of opinion. He wrote: "in the literature from 1940 through 1951, there were reported approximately 160 gliomas of the optic nerve or chiasm. Among these, 60 were in association with von Recklinghausen's disease, a percentage of 37.5. Yet, among the 160 most recent reports, in 81 no mention was made of whether or not von Recklinghausen's disease was otherwise evident, and in only 19 was the statement made either that the general physical examination was negative, or that there was no external evidence present of neurofibromatosis. There can no longer be doubt that the frequency of this tumor association far exceeds the reported instances." Marshall[54] went on to say that the incomplete form of von Recklinghausen's disease is very common, especially in children of diseased parents, for manifestations may be delayed in appearance until any time in the first four decades. A child may show only café-au-lait spots, or perhaps only an optic nerve glioma, and not develop skin tumors or other signs of the disease until some time later. A careful complete examination of the patient and his relatives is essential for the study of the relationship between optic nerve glioma and neurofibromatosis.

Another factor to be taken into account is disagreement as to the significance of café-au-lait spots. Crowe and Schull[13] stated that café-au-lait spots are of melanic origin, vary in size and configuration, may be single or multiple and are found especially on unexposed areas of the skin. They noted that there is no gross or histologic difference between the café-au-lait spot in the normal individual and that of von Recklinghausen's disease. Counting only spots with a broadest diameter exceeding 15 mm., Crowe and Schull[13] found that approximately 10% of normal individuals will have 1 to 5 café-au-lait spots. Ninety per cent of 98 persons with neurofibromatosis had from 1 to 26 or more café-au-lait spots. Among almost 7000 persons examined, not a single adult who did not have neurofibromatosis was found to have 6 or more of the spots. Crowe and Schull[13] reached the following conclusions: (1) any person with more than 6 café-au-lait spots which exceed 15 mm. in broadest diameter must be presumed to have neurofibromatosis even in the absence of a positive family history; (2) since 5 café-au-lait

spots are infrequent in normal persons, the probability that a person with 5 spots has neurofibromatosis is certainly higher than that of a person with only one spot; (3) "If a person has fewer than 6 café-au-lait spots but there exists a family history of neurofibromatosis, the possibility of involvement is a function of the similarity in macular pigmentation between this person and the affected persons in the family. More reliance should be placed on comparison of sib to sib than on comparison of parent to offspring."

In his text, Reese[60] estimates the percentage frequency of neurofibromatosis in optic nerve gliomas as about 10, a figure that was arrived at by Regoli. However, Levitt[44] noted that the association between the two lesions may be missed because 60% to 75% of optic nerve gliomas occur in the first decade of life while the peripheral manifestations of neurofibromatosis usually do not become evident until puberty or even later in life. And Braendstrup[8] added, "attention should therefore always be focused on neurofibromatosis manifestations both in the families and the patients themselves who suffer from opticus tumors, and they ought to be examined for abortive stigmata, as it must be borne in mind that the intensity of the peripheral and central affection often varies markedly in members of the same family." Levitt[44] ventured the opinion that "It is not impossible that in the future primary tumors of the optic nerve occurring without any other abormality will be considered the sole or initial manifestation of Recklinghausen's disease."

Dresner and Montgomery[23], in commenting on the cases they reported said, "Central neurofibromatosis manifesting itself as glioma of the optic chiasm in uniovular twins with von Recklinghausen's disease has never previously been reported. In our own patients (cases 1 and 2), whilst the hereditary nature of the peripheral neurofibromatosis is clear and appears to be transmitted as a Mendelian dominant factor, there is no such evidence as regards the chiasmal lesions, which appear to have arisen in this family for the first time." Dresner and Montgomery[23] said that optic nerve lesions had been found in 3 of 8 patients with von Recklinghausen's disease and they commented, "No conclusion can be drawn from such a small series, but we feel that if the syndrome is borne in mind, careful examination may reveal more cases of optic atrophy with von Recklinghausen's disease than have hitherto been recorded." Kirby[40] found 4 tumors of the optic nerve and 2 tumors of the chiasm among 20 cases of von Recklinghousen's disease with ocular lesions collected from the files of the Mayo Clinic.

Christensen and Ry-Andersen[11] stated that 6 of their 12 cases of glioma of the optic nerve or chiasm, or both, exhibited more or less pronounced symptoms of von Recklinghausen's disease. Manschot[52], who reported 2 cases of glioma of the optic nerve and chiasm in sisters in a family with von Recklinghausen's disease, stated that, while Bürki[10] had found that 12.3% of 430 cases of tumor of the optic nerve showed general neurofibromatosis, that percentage had risen to 37.6% of 93 cases reported since 1933. Davis[19] remarked in 1954 that he had collected by then 15 personal cases of glioma of the optic nerve or chiasm, or both, and that all of them were accompanied by peripheral signs of von Recklinghausen's disease, usually of the abortive type.

Taveras, Mount and Wood[71] found evidences of neurofibromatosis in only 3 of their 34 cases of glioma of the optic nerve and chiasm, though the mother of a fourth patient had the

disease. Walsh[77] found evidence of neurofibromatosis in 4 of his 26 patients with intrinsic tumors of the optic nerve and chiasm, but commented, "Dr. Davis feels that Marshall's figures of 16 per cent and mine of 15 per cent probably do not represent the full percentage chance of tumors of the nerve or chiasm being associated with or part of neurofibromatosis. I am inclined to agree." Walsh[76] added that glioma of the chiasm should always be suspected when a patient with von Recklinghausen's disease exhibits loss of visual acuity. Four of the 13 patients with gliomas of the optic pathways reported by Fowler and Matson[25] were placed in an intraorbital group; none of these showed evidences of von Recklinghausen's disease. Nine were placed in an intracranial group; 4 of these had evidences of von Recklinghausen's disease.

Though the percentage figures given vary considerably and are somewhat confusing, it would seem that most, certainly, of the authors quoted are inclined to the opinion that gliomas of the anterior visual pathways are one of the manifestations of von Recklinghausen's disease. It would appear that Dodge and his co-authors[20] dissent from this opinion. They[20] stated: "The thesis that gliomas of the optic nerve are but part of a complex which includes generalized neurofibromatosis and cerebellar and other tumors did not find confirmation in our study. Of our 46 patients, 9 displayed skin blemishes, which varied all the way from cutaneous hemangiomas to pigmented moles. In 6 patients they were called café-au-lait spots; yet in only one was there microscopic proof of an associated neurofibroma. One additional patient had a cerebellar astrocytoma successfully treated by surgical removal four years after extirpation of a glioma of the optic nerve. All "brain tumors" developing in the remaining patients gave symptoms of hydrocephalus from the anticipated or demonstrated involvement of the third ventricle secondary to proximal progression of lesions in the optic tract."

RADIOTHERAPY. Most writers on the subject seem to be agreed that some form of surgical attack is the preferred method of treatment of gliomas of the anterior visual pathways. Radiation therapy is reserved as a rule for use after surgery, particularly in those cases in which removal of the growth is impossible or incomplete, in the hope of preventing recurrence or further extension of the tumor. Its effect in these cases is difficult to evaluate. The use of radiation therapy for treatment of their cases after transfrontal craniotomy with or without biopsy or after intraorbital surgery was recorded by Grinker[29], Rucker[65], Slade and Weekley[67], Hartemann, Dureux and Algan[32], Saebo[66], Francois and Rabaey[26], Mann, Yates and Ainslie[51] and Hummelt[36]. Two of the 4 transfrontal cases included in the reports of these authors were known to be alive 1 year and 18 months respectively after surgery. Two of the 5 transorbital cases were alive 1 year and 13 months respectively after surgery. One of the transorbital cases died 1 year after surgery, apparently from intracranial extension. In the case reported by Mann, Yates and Ainslie[51], deep Roentgen-ray therapy was given in the hope of preventing recurrence after apparently complete removal of an intraorbital glioma of the optic nerve. A Roentgen-ray burn developed with extensive scarring of the lids and globe. Four years later, a highly malignant meningioma developed within the area of the burn. It was excised but recurred. The orbit was exenterated but, 8 months later, the tumor recurred again, this time with evidence of intercranial involvement.

Martin and Cushing[55] and Davis[18] thought that gliomas of the chiasm were inoperable and that deep Roentgen-ray therapy offered the most hope of arresting or limiting the lesion. Dresner and Montgomery[23] wrote that the treatment of intraorbital tumors is surgery but that operation is contraindicated in gliomas of the chiasm. Roentgen-ray irradiation may be attempted, but, as in other benign tumors, cannot be expected to accomplish much. Taveras[70] and Taveras and his co-workers[71] presented the most adequate available survey of the effects of radiation therapy on gliomas of the optic nerve and chiasm. They commented: "While it may be difficult to ascribe relative values to surgery and irradiation in the management of individual cases, experiences with tumor recurrences strongly point to the effectiveness of irradiation alone." They[70,71] reported on 34 cases, 19 of which were verified histologically, treated at the Neurologic Institute and the Institute of Ophthalmology with Roentgen therapy alone or combined with conservative surgery. Pneumography demonstrated suprasellar masses in 21 cases and when repeated after treatment in a number of cases showed remarkable shrinkage of the tumors. In the majority of cases, surgery was limited to verification of the lesion by gross inspection with or without biopsy. In 2 cases, the tumor did not reach the chiasm and was removed and Roentgen-ray therapy was given subsequently. Vision was still normal in the uninvolved eye 12 and 14 years later. In 4 others, the tumors were removed transorbitally and no radiation therapy was given. Three patients had shunt operations for the relief of obstruction to the foramen of Monro; all died within 2 to 5 months after surgery. Twenty-two patients were assessed with regard to 5-year survival. Seven had died, 3 within the immediate postoperative period. Fifteen patients were alive and well 5 to 22 years after radiation therapy. Eight of the 15 had restoration of lost vision or arrest of the advancing visual deficit. Seven showed advancement of the visual impairment in spite of treatment but no evidence of extension of the tumor beyond the optic nerve and chiasm, and their general health had remained good. In 7 cases, less than 5 years had elapsed since treatment. In the majority, there had been significant improvement with arrest or reversal of the visual changes. Only 2 of 7 patients with exophthalmos who had adequate Roentgen-ray therapy had to have surgical removal of the orbital tumor later. The exophthalmos receded completely in 3 cases and to a satisfactory level in the other 2.

Taveras and his co-workers[71] felt that surgery is indicated only for diagnosis, or to relieve obstruction to the circulation of the cerebrospinal fluid, or when exophthalmos has failed to respond to radiation therapy or possibly when the tumor is confined to the orbital portion of the optic nerve so that complete removal is possible. They stated, "Of the many and varied benefits received from radiation therapy, few are so dramatic as the restoration of vision. This remarkable result occurred in a significant number of our patients." They concluded that gliomas of the optic nerve and chiasm do not require radical surgery. They said: "Experience has produced a trend to conservative surgery, chiefly diagnostic craniotomy in obscure cases or relief of the obstruction of cerebrospinal fluid circulation which occurs in some patients. A possible exception to this general principle is the tumor which is confined to one optic nerve, allowing complete removal. Even in such cases a trial course of radiotherapy may

be in order prior to surgery. The results in this series in which irradiation alone not infrequently caused complete and permanent regression of an existing exophthalmos and, in a few instances, led to almost complete restoration of vision in an eye which was thought to be blind, seem to justfy this conclusion. The infrequent recurrence of optic gliomas following radiotherapy is remarkable." They added that surgery should be preceded by radiotherapy in cases in which an enlarged optic foramen indicates intracranial extension of an intraorbital glioma.

SURGICAL TREATMENT. Apparently Dandy[15] was the first to suggest the transfrontal intracranial approach to the removal of intraorbital tumors. He wrote in 1922, "Until now, the treatment of orbital tumors has been restricted to the removal of the intraorbital tumor. The future of the patient has then been left to chance. And we have seen from the ultimate results, as inadequate as they are, that a very high percentage of these patients die of an intracranial tumor. If it is found from autopsies and from reliable clinical data that most orbital tumors enter the cranium, then this intracranial operation (which combines the intraorbital also) will be found the safest procedure in the beginning, rather than to await the verdict of the operator who has done a local removal of the orbital tumor. . . . If either a primary intracranial tumor of the optic nerve or a secondary intracranial extension of an intraorbital tumor is present, only an intracranial operation which aims at the removal of the tumor offers the patient any chance of the preservation of life or vision."

In a paper presented in 1940, Dandy[16] said: "In 1921 I encountered by the cranial route an intracranial tumor that had extended through the optic foramen into the orbital cavity. The orbital roof was removed in order to follow and extirpate this portion of the tumor. So simple was the operative attack and so perfectly could the intraorbital contents be exposed that this method suggested great improvement in operative attack on the great group of orbital tumors. No matter in which direction the intracranial portion of the tumor extends or in which part of the orbit the tumor is situated, this approach has proved far superior to the usual frontal or lateral (Krönlein) routes by which such tumors had previously been attacked. . . . And even for the tumors that are confined to the orbit alone, this approach has been found to be preferable to those formerly used by the ophthalmologists." He added that the transcranial approach offers the only hope of a permanent cure when the tumor is in both cavities, and, when the condition is incurable, it offers the maximum palliative result. Apparently Dandy's[16] series did not include any gliomas confined to the intraorbital portion of the optic nerve. There were 4 cases with widespread growths involving the chiasm and one or both optic nerves within the cranial chamber and also in the orbits, and in each the brain was also involved. The orbits were not entered as the tumors were clearly inoperable. All 4 cases came to necropsy. In discussing Dandy's[16] paper, Knapp[41] said he felt convinced that tumors restricted to the orbital cavity could be taken care of by simpler and less dangerous procedures. In 3 cases with enlarged optic foramens, gliomas of the optic nerve were removed by the Krönlein technique. There was no evidence of intracranial extension after 15 to 17 years. Bair[3] said that most orbital tumors can be taken care of through the anterior or the Krönlein route. However, if there is roentgenologic or

other definite evidence of intracranial extension or origin of the tumor, such external approaches are not suited to adequate exploration or to removal of the tumor and the transfrontal intracranial approach by the neurosurgeon is indicated. Benedict[4] reported that the transcranial approach for the removal of orbital tumors had been employed at the Mayo Clinic in 48 of 420 cases between 1933 and 1947 with only one operative death. Twenty-eight of the tumors were entirely within the orbit, 17 had extended intracranially and 3 had invaded the adjacent bone. The remaining 372 cases were operated through an orbital approach. Benedict[4] wrote: "The entire orbit may be explored through a frontal approach, but the removal of a tumor originating in the posterior one third of the orbit or of a tumor of the optic nerve without removal of the eye is extremely difficult. If the transcranial approach is used, the task is less complicated."

Davis[18] utilized an incision at the lower rim of the orbit for his approach to the removal of the gliomas of the intraorbital portion of the optic nerve in his cases. He wrote: "The anterior orbital approach to the tumor is infinitely more simple and safe than the formidable transfrontal route. Unless there is evidence of chiasmal involvement or definite signs of massive extension of the tumor into the cranium, it would seem that some procedure of this type should be the method of choice." In discussing Davis'[18] paper, Bailey[1] said that the operative approach that Davis[18] used was logical and safe and effectively answered Dandy's[15,16] dogmatic disapproval of an ophthalmic approach to the removal of these tumors. He[1] commented that "No one who knows how little can be accomplished by intracranial operation could be enthusiastic about the transfrontal route." But Woods[80] stated in his discussion that he favored the transfrontal intracranial approach because of the intraorbital recurrences and intracranial extensions following the incomplete removal of the tumors by the orbital approach.

Jefferson[39] said that the neurosurgeon's approach to the orbit is a relatively simple procedure which carries no mortality and that it is very much superior to the external approach, not only from the point of view of cosmetic result but also because the actual approach to the tumor is better. He called attention also to the fact that neither in the case of meningeal tumors nor in that of intrinsic glial tumors of the optic nerve can it be determined clinically that the intraorbital portion is the only part involved by the tumor. Bucy, Russell and Whitsell[9] stated likewise that some authors reserve the transfrontal operation for cases with obvious involvement of the intracranial portion of the optic nerve. But, as intracranial extension may be present without enlargement of the optic foramen or other signs, by the time that involvement of the chiasm or invasion of the brain has become obvious, the tumor is already inoperable. They said further: "The principal disadvantage of the intraorbital approach is that it is never possible to expose and remove that portion of the optic nerve within the optic foramen and the intracranial cavity. Such exposure is important if the tumor is to be completely eradicated and if the mortality of these serious lesions is to be lowered." They favored the transfrontal approach in all cases of optic nerve tumor.

Dodge and his co-authors[20] said that the choice of the surgical approach to the orbit and optic nerve should be made after consultation between the ophthalmologist and neurosurgeon. They thought that the treatment of

gliomas of the optic nerve and chiasm should always be surgical and they added, "The transcranial surgical approach is, in our opinion, the most favorable approach. It provides better visualization and direct surgical verification, the opportunity for complete removal of localized lesions, with ultimate cure, and the chance of less cosmetic defect postoperatively. Enucleation of the eye or exenteration of the orbit seems unwarranted." Dodge and his co-authors[20] wrote also that the commonest transcranial approach to the orbit and optic nerve is via frontal craniotomy. Simultaneous exploration of both orbits and visualizaation of both optic nerves may be achieved by using a Souttar type of concealed scalp incision and a bifrontal craniotomy. Gliomas limited to one nerve can be excised completely. More diffuse tumors of the optic nerve and chiasm or tract can be surgically verified and resected to varying degree and, if necessary, exploration of the sella and pituitary can be done at the same time.

In spite of the apparent logic of employing the transfrontal intracranial operation for the surgical treatment of all gliomas of the optic nerve and chiasm, the majority of writers seem to favor a primary transorbital operation for gliomas of the intraorbital portion of the optic nerve unless probable intracranial extension of the tumor is demonstrated by enlargement of the optic foramen. This position was taken, for example, by Braendstrup[8], Reese[60], Christensen and Ry-Andersen[11], Streiff[69], Marshall[54], Davis[18], Hummelt[36], Dollfus[21], Oribe, Zimman and Franke[57], Hanberry[31], and Buerman and Tabor[6]. Wilson and Farmer[78] and Spaulding[68] apparently advocated combined transcranial and transorbital operations.

As is recorded in separate case reports, gliomas of the intraorbital portion of the optic nerve were removed transorbitally by Levitt[44], Donahue[22], Berg[5] and Jain[38]. In Donahue's[22] case, in spite of enlargement of the optic foramen, the orbital approach was used. The eye was enucleated and several millimeters of the optic nerve were excised. The orbit was exenterated 15 months later because of a recurrent mass in the orbit. Twenty years and 9 months later, a second recurrent mass was observed. There had been no symptoms suggesting intracranial involvement during all this time.

Transcranial surgery was done by Hanberry[31], by Craig and Dodge[12] and by Love, Dodge and Bair[49] for the extirpation of gliomas involving both the orbital and the intracranial portions of the optic nerve and by Manschot[52], Levitt[45] and Uihlein[72,73] for gliomas of the optic nerve and chiasm. Craig and Dodge's[12] patient was alive 8 years after surgery. One of the patients reported by Love, Dodge and Bair[49] was alive 1 year after surgery, another 9 years and a third 12 years after surgery. In Hanberry's[31] case, transfrontal exploration was carried out with removal of the roof of the left orbit. The tumor did not extend to the globe and did not involve the chiasm grossly. The involved segment of the optic nerve was resected in one piece. The globe was not removed. The patient died 8 months later following a second intracranial exploration done because of the complaint of headache and vomiting. Necropsy revealed a large glioma which appeared to originate from the optic chiasm and the floor of the third ventricle. Uihlein[72,73] had resected the right optic nerve and the right half of the chiasm of his patient. One year later, the right eye was blind, but central vision of the left eye was 6/5 and there was only a relative defect

in the upper temporal quadrant of the left visual field.

Transfrontal surgery with secondary enucleation of the eye and excision of the intraorbital portion of the tumor was done for the treatment of gliomas of the intraorbital and intracranial portions of the optic nerve by Rand, Irvine and Reeves[59], by McFarland and Eisenbeiss[56] and by Gramberg-Danielsen[28]. The patient operated on by Gramberg-Danielsen[28] had 5/7 vision and a normal visual field in his remaining eye 6 months after surgery. His general physical and neurologic examinations were negative.

Fowler and Matson[25] preferred the intracranial approach for removal of gliomas of the optic pathways. They described their method of proceeding in some detail. The roof of the orbit and the region of the chiasm are exposed transfrontally. If there are definite clinical signs of orbital involvement, the roof of the orbit is removed extradurally. If tumor is found in the nerve, resection up to the globe is done. Whether or not there is clinical evidence of intracranial extension, it is wise to open the dura and visualize the intracranial portion of the optic nerve and the chiasm. In most instances, it is best to resect the optic nerve back to the chiasm. On occasion, it may be possible to remove an involved portion of the chiasm itself if it is felt that this will insure complete excision of the neoplasm, even if vision is further impaired by so doing. If there is gross involvement of the entire chiasm or of the optic tract, it is best to remove only sufficient tissue for biopsy. If there is any remaining vision in the affected eye, a careful decompression of the optic canal and orbit should be done. It is possible to leave the eye in place if there is no neoplasm in the distal end of the optic nerve. Otherwise, the eye should be enucleated at a later date. In all of their patients, enucleation proved to be necessary to achieve complete excision of the tumor. Fowler and Matson[25] added this comment, "It would seem reasonable in our opinion, therefore, that if a glioma of the optic pathways cannot be completely excised, it would be well to give Roentgen therapy to the areas involved in the hope that it might be of some value in delaying further growth. Based on our own limited experience it cannot be assured that any improvement in neurologic status will take place after such treatment.

Walsh[77] listed the indications which guide him to the selection of the type of treatment to be used for individual cases of tumors involving the anterior visual pathways: "(1) If it is thought that the tumor is contained within the orbit, it can be removed by the ophthalmic surgeon through a classical Krönlein procedure or some modification of it. If it is recognized that the tumor is within the optic nerve, it is proper to obtain biopsy tissue. If the tumor is glioma, radiation may suffice to arrest the progress and cure the patient. If, in such an instance, the visual acuity is already lost or is extremely low, removal of the swollen segment of nerve may suffice and would be the method of choice. If the tumor is far posterior in the orbit, unless there is reason to believe that it has extended into the cranial cavity, removal and Roentgen-ray therapy is indicated, if the section shows glioma; (2) If the tumor is thought to be entirely within the cranium, the neurosurgeon should undertake the operative treatment. (3) If the tumor is thought to be both intracranial and intraorbital (and this is always the case if the optic canal is dilated), operation should be transcranial. The situation calls for combined efforts and the ophthalmic sur-

geon may be of great assistance when the orbit is unroofed. (4) It is the neurosurgeon's responsibility, if, after a transcranial operation has been performed, an enucleation or exenteration of the orbit is required, that the cerebrum does not herniate into the orbit. Limited unroofing of the orbit gives an unsatisfactory approach to the orbital contents. Insertion of a tantalum plate or some such maneuver is necessary after the orbit has been unroofed."

As both Fowler and Matson's[25] and Walsh's[77] reports were published within the last 2 years, it is apparent that there is still considerable variance of opinions as to the preferred methods of treatment of gliomas of the anterior visual pathways, especially of gliomas of the intraorbital portion of the optic nerve. To an impartial observer, it would seem that surgery is preferable to irradiation as a primary procedure and that the arguments in favor of the transfrontal intracranial approach are the more convincing. There appears to be general agreement that neurosurgery is necessary when there is clinical evidence of involvement of both the intraorbital and intracranial portions of the nerve. There is still some uncertainty as to what should be done when, on exploration, a primary glioma of the optic chiasm is encountered.

In speaking of primary gliomas of the chiasm and optic nerves in their intracranial portion, Martin and Cushing[55] said: "Unquestionably if we may come in time to perfect our clinical diagnosis of these lesions there is every reason to avoid operating upon them, though in cases of doubt an exploration may have to be made. Whether one would be justified in making a complete removal of the chiasm involved in one of these lesions is doubtful. X-ray therapy is probably our best hope." Cushing[14] said that gliomas of the chiasm "often come to involve the wall of the third ventricle with the production of hypothalamic symptoms and ultimately of hydrocephalus, but fortunately the lesion may be a slowly progressive one, long unaccompanied by any symptoms other than loss of vision. The condition can hardly be regarded as surgical except for the fact that pedunculated outgrowths from the nerves that serve to cause chiasmal pressure may be found and removed. A surgical exploration may therefore be justified if only precisely to determine what the local condition may be." Grinker[29] wrote that pure intraorbital tumors may be cured by complete excision but that intracranial involvement unfortunately can be treated only by deep Roentgen therapy, as operative intervention almost invariably causes death with hyperthermia. Jefferson[39] thought that intervention in gliomas involving the chiasm might do harm rather than good. Walsh[76] states that any tumor which originates in the optic nerve may arise also in the chiasm and it may be difficult to determine whether a tumor originates in the chiasm or in the optic nerve or as a suprasellar tumor. Radiation therapy may be beneficial in the treatment of tumors originating in the optic chiasm. Surgery precipitates bilateral blindness. Excision of the chiasm may result in fatal hyperpyrexia. He added that removal of the chiasm is contraindicated on two scores, immediate and total blindness and danger to life.

In writing about the surgical treatment of gliomas of the optic nerve and chiasm, Marshall[54] stated: "To operate upon the chiasm is not only dangerous to the visual pathways but is often fatal because of damage to vital centers. To attempt to remove a glioma of the optic nerve in the short distance between the foramen and chiasm, without endangering the chiasmal region, cannot effect a thoroughly complete

excision, and therefore gains little. The transcranial approach to an intracranial glioma of the optic nerve or chiasm becomes indicated, therefore, for diagnosis or to unroof the optic canal, and to open the nerve sheaths and allow expansion. To attempt more, especially in the presence of von Recklinghausen's disease, would seem, usually, to be unwise." And according to Levitt[45], "there is general agreement in this country that glioma of the optic chiasm is not amenable to surgery, as complete removal of the lesion is impossible and mortality is high when operation is attempted. Roentgen therapy is favored as offering the only possible hope of arresting the growth."

On the other hand, as previously noted, Fowler and Matson[25] stated that it was possible at times to remove an involved portion of the chiasm itself and Uihlein[72] successfully resected the right half of the chiasm in a case reported in association with Rucker[73]. Christensen and Ry-Andersen[11] stated that operation resulted in marked improvement in their 6 cases of glioma involving the chiasm. Only 2 of the 6 patients had recurrences and died, one not until 12 years after the operation. Personally, I can recall at least 1 case in which resection of the involved portion of the chiasm apparently stopped the progression of the glioma. But the difficulties and complications encountered in operations on cases of glioma of the chiasm and the intracranial portion of the optic nerve are illustrated in the group of patients studied by Dodge and his co-workers[20]. There were 14 cases of glioma of the chiasm, in 6 only biopsy was done and in the other 8 it was doubtful that complete removal of the tumor was accomplished. Follow-up studies were possible in 9 cases. Three patients had died with clinical evidence of extension into the brain and such extension was found at necropsy in another patient. Three of the remaining patients had obstructive hydrocephalus. There was diffuse involvement of the chiasm and tracts in 20 cases, bilateral in 17. Posterior extension of the neoplasm was such as to prevent total removal; subtotal removal was attempted in 5 cases. There was obstruction of the third ventricle by neoplastic tissue in 7 cases. Six patients came to necropsy.

PROGNOSIS. Craig and Dodge[12] noted that survivals for as long as 20 years after mere biopsy of a glioma of the optic nerve are well documented. And Hudson[35] remarked that cases of glioma of the optic nerve have been followed for as long as 24 years without recurrence even after incomplete removal. However, Rand, Irvine and Reeves[59] stated that, although the possibility of recurrence in the orbit is remote after complete removal of an intraorbital glioma, incomplete removal is unjustifiable, especially as there is no evidence that subsequent slow extension along the nerve to the brain is inhibited by partial removal of the intraorbital tumor. Craig and Dodge[12] stated also that a glioma of the optic nerve is a notoriously slow-growing or recurring tumor. There can be no "false sense of security" in respect to such a lesion. Walsh[76] states that gliomas, although usually slow-growing tumors, vary in their rate of growth and that it is generally agreed that, if untreated, they all finally result in death. Hanberry[31] wrote that gliomas of the optic nerve are slow growing neoplasms and that survival rates up to 24 years have been recorded for cases that received adequate surgical treatment. He said: "Prognosis is excellent for those cases in which the neoplastic growth is confined to one optic nerve if excision is complete. Even when intraorbital optic nerve gliomas have been incompletely removed, survival rates are usually

measured in years, although the patient usually succumbs eventually to intracranial extension." Mann, Yates and Ainslie[51] agreed that gliomas of the optic nerve are slow growing and added that they do not metastasize. If the tumor is completely removed, the prognosis is good. Death, when it occurs, is from intracranial extension and may be delayed for many, even up to 26, years. In the course of a discussion on tumors of the optic nerve, Hudson[35] said: "As to expectation of life the data available are too scanty to be of much value, except insofar as they indicate the gravity of signs of involvement of the chiasm by a glial tumor." In all of the 13 cases in which death occurred under observation (at periods of 1 month to 4 years after the patient was first seen) and in 3 cases in which death occurred immediately after operation, there were symptoms of chiasmal or other intracranial disease.

The difference between the postoperative prognosis of gliomas confined to the intraorbital portion of the optic nerve and that of those with involvement of the intracranial portion and of the chiasm is demonstrated in the groups of cases studied by Fowler and Matson[25] and by Dodge and his co-workers[20]. All of the 4 patients in Fowler and Matson's[25] intraorbital group were living and well 1 month to 8 years after surgery and had normal vision in their remaining eye. Two of the 9 patients in their intracranial group died after biopsy of the lesion. Seven were living 1 month to 7 years after surgery. One was blind and 6 had useful vision. In 1 patient it was necessary to do bilateral ventriculocisternostomy because of blocking of the anterior portion of the third ventricle.

Dodge and his co-workers[20] stated that their studies indicated an excellent prognosis for unilateral lesions of the optic nerve, with so-called cure following total removal. The more diffuse tumors, which involved the optic chiasm and tracts, carried a less favorable prognosis. The natural long life of many of the patients with minimal treatment has to be taken into account, they stated, in the appraisal of any kind of treatment for tumors of this type. Eleven of their 12 patients in whom gliomas of the optic nerve were resected surgically, were living 1 to 27 years after the operation. One patient died 4 years after surgery of an unrelated brain tumor. Of the 34 patients in whom biopsy or partial resection of gliomas of the chiasm and intracranial portion of the optic nerves was carried out, 13 died within 5 years after surgery, 8 during the first year. Twenty were living 1 to 15 years after surgery. One patient could not be traced.

I have been interested personally in the ophthalmoscopic appearance of the ocular fundus in cases of glioma of the optic nerve after section of the nerve at the posterior surface of the globe. In the immediate postoperative period, the retinal vessels are bloodless and barely visible in some instances, whereas they appear to be normally filled in others. Descriptions of the postoperative appearance of the fundus is given in only a few of the reported cases. Verhoeff[74] recorded the late development of chorioretinal atrophic and pigmentary degenerative changes in several of his cases and additional retinitis proliferans in one. Hummelt[36] removed the optic papilla along with the nerve stem in his case; this resulted in total detachment of the retina.

In one of Davis'[18] cases, preoperatively, the disk was elevated 2 diopters and its margins were blurred. Immediately postoperative there was increased

congestion of the disk. Six days later, the vessels were full and of normal caliber and the color of the disk had not changed. Two years later, the vision was nil and there was total atrophy of the disk. The retinal vessels were slightly constricted but contained blood. There were no hemorrhages, exudates or pigmentation. In another of his cases, preoperatively, the disk was pale. Six months after operation, the disk was pale, the retinal vessels were narrow and apparently bloodless. There was extensive degeneration of the retinal pigment. Davis[18] noted that the postoperative ophthalmoscopic findings in the first of these cases demonstrated that the retinal vessels do not always collapse after the optic nerve is severed. He thought, correctly probably, that circulation was maintained in the retinal vessels through anastomoses between the ciliary and the retinal systems. The ciliary arteries arise from the ophthalmic artery outside of the nerve. The absence of the typical late pigmentary degeneration of the retina was thought to indicate that this layer of the retina was well nourished also.

Marshall[54] stated that 4 days after the excision of an astrocytoma of the optic nerve that extended from the globe to the apex of the orbit there was "a large white area of retinal edema in the region of the optic disc. This gradually cleared but 8 days postoperatively the area of the disc still was edematous and there were hemorrhages and edema at the macula. Two weeks after surgery veins and arteries in the retina appeared to be almost the same in color, and both, except near the disc, showed segmentation and gaps in their blood columns. Nasally and below, there was much atrophy and depigmentation of the retina. The macular area was still edematous. Some vessels appeared only as white streaks. Two and one-half years after surgery, the right lens and vitreous were clear. Disc markings were completely obliterated by an overlying white film of glial tissue. Most of the retina showed severe atrophy and pigment clumping, but, from a point below the macula, the lower retina had a normal appearance except for extremely attenuated retinal vessels."

In Hanberry's[31] first case, preoperatively, the nasal margin of the optic disk and the neighboring retina were elevated 4 to 5 diopters and there was wrinkling of the retina suggesting pressure from a retrobulbar mass. Postoperatively, the optic disk showed marked atrophy and there was pallor of the entire retina and constriction of the retinal vessels. In the proptosed eye of Jain's[38] patient, the optic disk was atrophic and edematous and the retinal vessels were engorged and tortuous. Four days after excision of an oligodendroglioma of the optic nerve, the retina was completely ischemic.

Summary. The determination of the nature and extent of a primary tumor of the anterior visual pathways is difficult or impossible in many cases without an exploratory operation. Transfrontal craniotomy with removal of the roof of the orbit gives more information more readily than does an anterior orbital exploration. Also it affords more chance for complete removal of the tumor if its location makes it amenable to surgery. Most of the gliomas of the anterior visual pathways are low-grade astrocytomas. The prognosis is good if the tumor does not involve the chiasm and can, therefore, be removed completely. An astrocytoma of the chiasm presents a serious threat to vision and ultimately to life. Removal is often impossible and the effects of Roentgen therapy are uncertain. The

weight of available evidence seems to support the contention that astrocytomas and oligodendrogliomas of the optic nerve and chiasm are in some way a part of the von Recklinghausen disease syndrome.

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PHYSIOLOGY

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The Physiological Society of Philadelphia

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SEMINAR ON SYNAPTIC AND NEUROEFFECTOR TRANSMISSION

Introductory Remarks. GEORGE B. KOELLE, PH.D., M.D. (Department of Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania).

Five years ago this Society sponsored a Symposium on Neurohumoral Transmission, subsequently published[1], which was truly a historic occasion. Following historical surveys by the two outstanding leaders in the field, Prof. Otto Loëwi and Sir Henry Dale, a series of papers by an international group of participants reviewed practically all the major aspects of the subject. The considerable amount of further progress that has been made in the short time since then was brought out in two quite recent symposia, one on mechanisms of conduction and transmission[2], and the other on the catecholamines[3]. Tonight it will be our good fortune to hear three investigators whose work exemplifies the current status of several important phases of neurohumoral transmission. Dr. Grundfest will discuss the general properties of transmission at all synapses, and the evidence for its primarily chemical mediation. Ionic permeability changes which accompany neuromuscular transmission will be described by Dr. Nastuk. Dr. Dempsher will relate some properties of the ganglionic synapse which have been revealed by the use of a unique tool, the pseudorabies virus. There is no doubt that all the speakers will touch on several controversial issues; a lively, perhaps impassioned, discussion should follow!

Of all the proposed transmitting agents, the most extensively studied and best understood is acetylcholine (ACh). Nachmansohn has pointed out that at least three proteins are involved in its immediate functioning: the enzymes by which it is formed (choline acetylase, ChAc), and destroyed (acetylcholinesterase, AChE), and the receptor with which it reacts. Whereas direct attempts to investigate the nature of the receptor have been made only recently by Chagas and his associates, ChAc and AChE have been fairly well characterized. Recent work by our own group suggests that the latter is synthesized within the endoplasmic reticulum of the neuron, then transported through the axon to its functional site at the axonal terminations. Here it is likely that the primary function of AChE is the protection of the post-, and possibly the pre-synaptic site against ACh liberated quantum-wise during the resting stage; the immediate participation of AChE in the actual process of transmission is less certain.

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General Physiology and Pharmacology of Synaptic Transmission. HARRY GRUNDFEST, PH.D. (Department of Neurology, College of Physicians and Surgeons, Columbia University, New York).

Many physiological and pharmacological differences characterize conductile and transmissional activity in all animals. In all, these differences can be accounted for by a single factor, the difference in the reactivity of the electrogenic membranes involved in these activities[1,2,3]. A sequence of electrically excitable, potential-determined and self-limiting processes generates pulses of fixed duration, the all-or-none, decrementlessly propagating spikes of conductile membrane. The receptive membranes of most sensory cells and of synapses are electrically inexcitable. Their electrogenesis is graded, sustained, non-propagating, and may be of either sign. Depolarizing generator or postsynaptic potentials elicit a sequence of impulses in electrically excitable membrane when they carry information in a frequency-number code throughout the extent of the cell. Hyperpolarizing p.s.p.'s inhibit these excitatory effects, and they are important modifiers of complex activity as in muscle fibers of crustaceans and in nervous systems.

Synaptic electrogenesis, obligatorily chemically initiated, must involve release of small quantities of transmitter agents by secretory processes of presynaptic terminals. It is also specifically susceptible to small quantities of other chemicals, synaptic drugs. These pharmacological agents may be classified as synapse activators, mimetics of the transmitters, or as inactivators which block synaptic activity[2,4]. In turn, each class may be subdivided into drugs which affect both excitatory and inhibitory synapses or those which act selectively on one or the other type of synapse. Discovery and characterization of the synaptic actions of the ω-amino acids and related substances[5] has disclosed still further subdivisions. These agents act only upon axodendritic synapses of the vertebrate central nervous system. They do not affect axosomatic synapses nor the skeletal neuromuscular synapses.

In the vertebrate, the amino acid drugs are inactivators, the shorter chain compounds (C_2 to C_5) of depolarizing axodendritic synapses, and the longer (C_6 and above) of the hyperpolarizing. The latter are convulsant agents, like strychnine, which also blocks inhibitory synapses. Crustacean synapses are also affected by ω-amino acids[6,7], but in a characteristically different manner. The short chain compounds activate inhibitory synapses of lobster muscle fibers[8]. The long chain compounds and also strychnine are ineffective. However, carnitine which is a convulsant in the cat activates the excitatory synapses of lobster muscles. Picrotoxin, in the cat an activator of excitatory synapses, in the crustaceans blocks selectively the inhibitory synapses and is a competitive antagonist of the short chain ω-amino acids.

Thus, there is a doubly inverted relation between axodendritic vertebrate and invertebrate neuromuscular synapses. Inactivators of depolarizing in cat, activate the hyperpolarizing in lobster; an inactivator of hyperpolarizing in cat activates the depolarizing in lobster; an activator of depolarizing in cat inactivates the hyperpolarizing in lobster. This relation indicates that, despite phylogenetic differences, the various excitable membranes probably derive from substances of similar molecular structure.

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Ionic Factors in the Permeability Change Produced at the Motor End-Plate by Acetylcholine. WILLIAM L. NASTUK, PH.D. (Department of Physiology, College of Physicians and Surgeons, Columbia University, New York City). It has been shown (**Nastuk, W. L.,** Am. J. Med., **19**, 663, 1955) that the depolarization produced by microelectrophoretic application of acetylcholine to the muscle end-plate membrane, is almost completely prevented when all sodium chloride is removed from the extracellular fluid surrounding a frog sartorius muscle. In these experiments sucrose was substituted for the sodium chloride resulting in a lowering of the ionic strength of the extracellular medium. Presently reported experiments show that the loss of depolarizing power of acetylcholine as stated above is not to be explained on the basis of receptor insensitivity created by exposure to low ionic strength "sucrose-Ringer" because in this medium it is shown that receptors can react with acetylcholine and in turn become inactivated with time. Results of other experiments can be interpreted as showing that the permeability change at the acetylcholine activated end-plate favors transmembrane movement of potassium ions; the possibility that chloride ion permeability is also increased transmembrane passage of at least one additional ion whose identity is unknown at present. A final set of experiments was designed to test the movement across the acetylcholine activated end-plate membrane of cations whose diameter increased progressively. Ions such as phenyltrimethylammonium, and diethyldiethanolamine do not penetrate, while choline, tetramethylammonium dimethyldiethanolamine and trimethylethylammonium do so. This evidence can be taken as indicating that membrane receptor activation produces enlarged channels in the membrane through which ions may move more freely. It argues against a complete "breakdown" or disruption of molecular configuration in the membrane.

Transmission in Sympathetic Ganglia of the Rat. JACK ZABARA, TADASU TOKUMARU, M.D., and JOHN DEMPSHER, M.D. (Departments of Physiology and Pharmacology, School of Medicine, University of Pennsylvania, Philadelphia, Pa.). Spontaneous impulses are discharged over pre- and post-ganglionic nerves of superior cervical ganglia of rats infected with pseudorabies virus via the intra-ocular route. The activity originates in the presynaptic nerve endings and is discharged antidromically in the preganglionic nerve and orthodromically in the postganglionic nerve. The activity in each nerve consists of a slow decrementing potential change at the peak of which appear rapid, non-decrementing potential changes. The slow potential change in the preganglionic nerve evidently originates in the presynaptic nerve endings since it decrements away from the ganglion, and is present whenever the virus kills off the postsynaptic cells. Gamma amino-butyric acid (GABA), epinephrine and norepinephrine depress the activity in both nerves simultaneously and synchronously as if acting on the pacemaker in the presynaptic nerve endings. Thiosemicarbazid and choline 2-6 xylyl ether bro-

mide (known to inhibit the formation of GABA, epinephrine and norepinephrine) cause an increase in activity over both nerves, again as if acting on the presynaptic nerve endings. In early infections whenever no activity is discharged in a ganglion *in situ*, removal of the influence of the CNS by sectioning of, or application of cocaine to, the preganglionic nerve results in the appearance of antidromic activity in that nerve. These experiments are interpreted in the following manner. In the peripheral sympathetic system of the rat there is an inhibitory component which originates in the CNS and exerts at the presynaptic nerve endings. Likely transmitters released by this system are GABA, epinephrine and norepinephrine.

BOOK REVIEWS AND NOTICES

A Short History of Anatomy and Physiology from the Greeks to Harvey. By Charles Singer, M.D., Emeritus Professor of Anatomy, University College, London. Pp. 209; 20 ills. New York: Dover Publications, Inc., 1957. Price, $1.75.

This book, originally published under the title *The Evolution of Anatomy* in 1925, is now reissued with a new preface by the author. A scholarly work on the early history of anatomy and physiology, it had long been out of print. The present edition, a paper-bound volume, is technically attractive and reasonable in price.

The author traces the evolution of anatomy from prescientific times through the Greek and Roman periods, the Dark Ages and the Renaissance, up to the time of William Harvey and the beginnings of modern scientific concepts. Primary attention is centered on individuals, movements and periods that advanced anatomical and physiological knowledge.

An excellent text amplified by carefully selected illustrations, Dr. Singer's work remains a classic in its field. In his preface to this second edition, he states, "The literature in English is now more copious than it was when the first edition was published over thirty years ago. Works by some of the leading figures in the history of anatomy . . . are now available in English translation, and I am in hope that this new edition may turn the reader's attention at least to these."

F. R.

Bases Physio-Biologique et Principes Generaux de Reanimation. By H. Laborit, Maritime Hospitals. Pp. 274; 61 ills. Paris: Masson et Cie, 1958. Price, 2.600 fr.

This volume is designed as the first of a series addressed not only to the specialist but also to the practicing physician. They will (according to the author) seek to outline in simple form the laws which govern the physico-chemical equilibria in the intracellular and extracellular environments of the body cells.

The chapter headings give some idea of the contents: 1) Cellular phenomena; 2) Physiologic phenomena; 3) Regulation of water and osmotic balance; 4) Regulation of acid-base equilibria; 5) Methods of investigation of ionic and metabolic phenomena; 6) Methods of elimination of hydrogen ions from the body; 7) The respiratory system; 8) The renal system; and 9) The cardiovascular system.

In addition to these and others, the effects of hypo- and hyperthermia in the treatment of disease states is discussed at length, from the point of view that treatment should be designed to assist the organism to re-establish the normal mechanism of organic regulation of the internal environment. It is stressed that re-establishment of regulation may result in equilibrium states not previously within the range of normal variation.

Some of the discussion is elementary, as it is designed to be. Some of the arguments are polemic and defensive. The volume will serve a useful purpose in redirecting attention from the all too prevalent treating of symptoms to the preferable goal of treating the patient. Further volumes are in preparation: Neuropsychiatric applications and Surgical applications.

J. B.

A History of Public Health. By George Rosen, M.D., Ph.D., M.P.H., Professor of Health Education, Faculty of Medicine, Columbia University; Editor, American Journal of Public Health. Pp. 551. New York: MD Publications, Inc., 1958. Price, $5.75.

This volume, the first in a series of monographs on medical history, is a readable account of the evolution of community health measures over the centuries. From the earliest civilizations to the present, groups of people have endeavored to cope with health problems in an organized fashion. Such problems include the control of communicable diseases, provision of water, food and shelter, disposal of wastes and caring for the young, aged and infirm.

Dr. Rosen, an expert in public health, approaches the subject from a broad point of view and considers the health problems of various peoples at different times in terms of their political, social and economic patterns. The lives and contributions of leading figures in public health are accordingly projected upon a broad tapestry of history. A selected bibliography and professional ref-

erence lists add to the usefulness of this book.

A History of Public Health will prove of value to all persons interested in public health, sociology and medicine. It will be particularly valuable to workers in the health professions directly concerned with the development of this important facet of our complex civilization. F. R.

PSYCHOENDOCRINOLOGY. Edited by MAX REISS, M.D., D.Sc., Neuroendocrine Research Unit, Willowbrook State School, Staten Island, New York, with 23 Contributors. Pp. 208; 36 ills. New York: Grune & Stratton, Inc., 1958. Price, $7.00.

PSYCHOENDOCRINOLOGY is the name used for the study of the interrelation between functions of the brain and the endocrines. Prior to World War II, much haphazard research had been done in this field. Unjustified claims were made which could not be validated. As a result, the study of endocrine psychiatry largely disappeared. Ten years ago, researchers began to make cautious, careful investigations in an effort to restudy previous work.

This small volume consists of sixteen papers, some clinically oriented, others experimental and biochemical in approach. The functions and dysfunctions of the endocrine glands have been studied in the mentally ill. No conclusions are drawn, other than that many interesting facts have been discovered and much research remains to be done.

This book is recommended to endocrinologists and psychiatrists, so that each may better understand the thinking of the other and better communication will ensue.

H. D.

ALLERGIE. Edited by PROF. DR. K. HANSEN. 3rd ed. Pp. 1212; 305 ills., some in color. Stuttgart: Georg Thieme Verlag, 1957. Price, $44.50.

THE term "allergy" was coined by Pirquet in Austria in 1906. The clinical concept of allergic disease had its first major impetus in the United States in 1910 when Meltzer suggested a relation between anaphylaxis and asthma. The development of allergy in its early years took place almost entirely in this country; indeed, allergy was largely ignored by clinicians on the European continent. That this has at long last completely changed is shown by this third edition (the second was in 1943) of what has become an exhaustive treatise on the subject. Twenty-four authors have contributed to the work, which is well ordered and is largely in agreement with current thinking in the field in North America. There are even a fair number (as German textbooks go) of references to the American literature, by far the most extensive. This text can hold up its head in any company. Allergists who read German will find here much that is useful. R. K.

ANATOMIST AT LARGE. AN AUTOBIOGRAPHY AND SELECTED ESSAYS. BY GEORGE W. CORNER, M.D., Sc.D., Historian, Rockefeller Institute for Medical Research. Pp. 215. New York: Basic Books, Inc., 1958. Price, $4.00.

THIS interesting volume stems from the life and work of one of America's foremost men of science. Dr. Corner, formerly Professor of Anatomy at the University of Rochester School of Medicine and Director of Embryology at the Carnegie Institution in Washington, D.C., has selected ten papers and addresses from his writings and prefaced them with a brief, personal autobiography.

Best known for his contributions to our knowledge of mammalian anatomy and physiology, with particular emphasis on human reproduction, the author's career has been a long and distinguished one. This book documents his role as scientific investigator, educator, historian and philosopher of science. His autobiography, 'Anatomist at Large,' chronicles fifty years of work in medical research and education, in a warm and honest fashion. The varied essays which follow initially appeared in print between 1915 and 1957. They range in topic from the author's discovery of the hormone progesterone to the ills of Benjamin Franklin.

A well-written and technically attractive book, *Anatomist at Large* is highly recommended for the interested reader. F. R.

A SEARCH FOR MAN'S SANITY: THE SELECTED LETTERS OF TRIGANT BURROW. Prepared by Editorial Committee of the Lifwynn Foundation, WILLIAM E. GALT, Chairman. With Biographical Notes and Foreword by SIR HERBERT READ. Pp. 615. New York: Oxford University Press, 1958. Price, $8.75.

THE letters in this volume were selected and prepared by the Editorial Committee of the Lifwynn Foundation which was founded by Trigant Burrow.

Dr. Burrow is one of the lesser known of the men who deviated from the main group of orthodox psychoanalysis. He was trained both as a psychologist and as a physician and for several years studied with Dr. Jung in Zurich. He practiced psychoanalysis in the United States and was President of the American Psychoanalytic Association in 1926.

During the years in active practice in psychoanalysis he became dissatisfied with the emphasis psychoanalysis placed on the individual and he gradually came to the belief that behavioral disorders were essentially social rather than individual. His letters trace the development of his thinking and have a strikingly wide range.

Of great interest are the letters to Freud pointing out the reasons for Burrow's disagreement with individual psychology and the letters to D. H. Lawrence acknowledging Lawrence's appreciation of Burrow's work. The man that emerges from these pages is a kindly, sensitive, but troubled human being who made an extraordinary effort to propound truth as he saw it. He was not only hurt, but bewildered, by the lack of universal acceptance of his own creativity. Many of his ideas have been incorporated in concepts of group therapy.

This book will be of special interest to sociologists and psychoanalysts but of general interest to those interested in a sensitively portrayed autobiography. R. L.

HEALTH YEARBOOK, 1956. Compiled by OLIVER E. BYRD, ED.D., M.D., F.A.P.H.A., Professor of Health Education, Stanford University. Pp. 278. Stanford, Calif.: Stanford University Press, 1957. Price, $5.00.

HEALTH YEARBOOK, 1957. Compiled by OLIVER E. BYRD, ED.D., M.D., F.A.P.H.A., Professor of Health Education, Stanford University. Pp. 278. Stanford, Calif.: Stanford University Press, 1958. Price, $5.50.

THESE are respectively the 14th and 15th volumes in a series that was begun in 1943. The author has abstracted 254 and 253 articles in the two issues here listed, culled from over 2,000 articles read in some 300 journals dealing with various aspects of health. The abstracts are grouped in 20 chapters under these headings: Health as a Social Accomplishment; Health as a Social Problem; Nutrition and Health; Mental Health and Disease; Heredity and Eugenics; Physical Fitness; Infection and Immunity; Chronic and Degenerative Disorders; Habit-forming Substances; Sight, Hearing and Speech; Dental Health; Safety and First Aid; Health and the Physical Environment; Health Services and Facilities; Family Health; School Health; Occupational Health; Community Health Services; International Health; Trends and Possibilities. At the end are the references to the original articles and a complete subject and author index. As these headings show, the contents are of interest to all, both lay and professional, who are engaged in any phase of public health activity. They will find here much useful material in convenient form.

R.K.

REGISTER DER WELTLITERATUR ÜBER VITAMINE UND DER VON IHNEN BEEINFLUSSTEN GEBIETE, VOL. II, 1930–1945. Edited by DR. M. STECHOW. Pp. 576. Würzburg: Physica-Verlag, 1956.

THIS volume, in three parts, is the direct continuation of Volume I, which covered the World Literature on Vitamins between 1900 and 1930. The rapidly increasing bulk and complexity of medical literature is well illustrated by comparing the 10,000 references in the first volume, covering a period of 30 years, with the 42,000 publications in 16 years listed in the second volume. The material is arranged by subject in 35 main divisions and about 1100 subdivisions in each of which the individual references are listed alphabetically by name of author. It is clear that such a compilation renders a valuable, indeed an indispensible, service to the scientist, investigator and clinician. It should be in every working medical library. R.K.

VERTIGO AND DIZZINESS. By BERNARD J. ALPERS, M.D., SC.D.(MED.), Professor and Head, Department of Neurology, Jefferson Medical College. Pp. 120; 4 ills. New York: Grune & Stratton, Inc., 1958. Price, $5.00.

THIS monograph on Vertigo and Dizziness should be required reading and in the library of every practitioner of medicine. It is an excellent presentation of a universally met and difficult symptom by an outstanding man in his field, a neurologist. The attempt has been made the author says, to present the problem in a practical fashion and in this he has eminently succeeded. Since, as he says, much remains to be learned, this book serves as a very adequate point of departure for all workers concerned. More than eleven pages of references are given for ready reference for further reading.

Sections are devoted to the anatomy and

physiology of the labyrinth and vestibular system. In this connection some of the printing on the illustrations might have been a trifle larger. The mechanism of the production of vertigo, the symptoms and signs associated with vertigo, the causes of vertigo and the diagnosis and treatment of vertigo are all given succinct and very readable consideration. The reviewer was particularly appreciative of the emphasis put on a careful and adequate history, the need for a sympathetic and understanding attitude by the doctor for the patient, and the fact that the Barany does not contribute very much to the management of the problem. The index is quite adequate.

In short, this reviewer enjoyed the experience and heartily recommends the book to all who are interested in the subject and who can fail to be in that group? S.G.

Old Doc. By O. H. Perry Pepper, M.D. Pp. 247. Philadelphia: J. B. Lippincott Co., 1957. Price, $3.75.

A retired Professor of Medicine (Doctor Pepper) writes charmingly of a retired professor of medicine (Old Doc) who, bereft of wife and work, returns in the evenings to the interns' smoking room of the hospital in which he (Old Doc) had spent his active years. There are delightful discussions in which he (Old Doc) tells the young doctors of the medicine of years gone by. He (Doctor Pepper) weaves into the story many a bit of sound clinical lore and the art of medicine, spiced with lighter reminiscences (Old Doc's, that is). Everyone and especially physicians will enjoy this fine story and look eagerly for another from the same pen. R.K.

Financing Health Costs for the Aged. New York State Conference Convened by Governor Averell Harriman at Albany, 1955. Pp. 239; 1 ill. Albany: State of New York, 1957. Price, $2.00. (May be obtained from the Office of the Special Assistant, Problems of the Aging, State Capitol, Albany, N.Y.)

The most pressing problem in the field of gerontology is the economic aspect of health protection and medical care for the aged. This volume is the record of a Conference, convened in Albany by Governor Harriman of New York, to discuss this problem. The conferees, some 68 in number, represent a wide range of interests: medicine, insurance, economics, hospital and institutional management, public health administration, labor and industry, legislation and government. All readers, lay or professional, who are concerned with any aspect of gerontology will find here much useful factual material and much varied discussion, valuable even though there are the inevitable political biases in the picture. R.K.

Mental Health in College and University. By Dana L. Farnsworth, M.D. Pp. 244. Cambridge, Mass.: Harvard University Press, 1957. Price, $5.00.

Here is an important pioneering contribution in the rapidly growing field of student health work. It is written primarily for educators but it will be valuable for all psychiatrists and particularly for the parents of college students. The chapter headings give a good insight into the scope of the work: Colleges Discuss the Need for Mental Health; Emotional Maturation of the College Student; Student Customs, Morale, and Attitudes; Emotional Stress in the College Students; Counseling and Psychotherapy; The Administration and the Psychiatrist; Development of College Mental-Health Programs; Emotions and the Curriculum. The author brings to his task a rich background of experience: Member and eventually Chief of the Student Health Service of Williams College; then Chief of the Student Health Service of Massachusetts Institute of Technology; now Oliver Professor of Hygiene and Director of University Health Services, Harvard University; also five years of active duty in the U.S. Navy in World War II. The book is well written: the style is clear and forthright, and shows a commendable lack of technical jargon that so often cloys psychiatric texts. The book is highly recommended. R.K.

Thannhauser's Lehrbuch des Stoffwechsels und der Stoffwechselkrankheiten. Edited by Nepomuk Zöllner, Privatdozent für Innere Medizin, München. 2nd ed. Pp. 1040; 230 ills. Stuttgart: Georg Thieme Verlag, 1957 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $30.25.

The reviewer wishes there were space to give in full the introductory letter by Dr. Thannhauser, author of the first edition (1929) of this work which bears his name. It tells of the status of the knowledge of metabolism a generation ago, when the chemical composition of organic matter had been rather generally determined and the science

of metabolism was a nicely detailed mosaic picture. That picture suddenly came to life with the discoveries in the mechanisms of enzyme reactions and in the nature and function of coenzymes and in the knowledge of intermediary metabolism. These and many other factors have so extended and complicated the field that one man can no longer write authoritatively on the whole subject: indeed, a new generation must take over. This edition is written by 15 authors, many of them former students and associates of Dr. Thannhauser. Further testimony to the breadth of modern science is the fact that of these authors, 5 are in the United States, 7 in Germany, 2 in France and 1 is in Sweden. It should be emphasized that this text includes the clinical and therapeutic as well as the chemical and physiologic aspects of metabolism and metabolic disorders.

There are sections on Total Metabolism, including Obesity and Malnutrition; Intermediate Metabolism, including avitaminoses and thyroid disorders; Metabolism of Carbohydrates and Diabetes Mellitus; Metabolism of Proteins and Aminoacids and Disorders of Metabolism of Amino Acids; Metabolism of the Mucopolysaccharides; Nuclein Metabolism and Gout; Metabolism of the Neutral Fats and Fatty Acids; of Lipoids; of Steroids and Carotinoids; of bile acids; of blood and bile pigments; Blood Coagulation; Iron Metabolism; Metabolism of Calcium and Phosphate; of Water and Electrolytes. There are numerous references to the important literature. The work is throughout of a high order of excellence: it deserves an English translation.

R.K.

KNOCHENSTRUKTUR ALS VERBUNDBAU. VERSUCH EINER TECHNISCHEN DEUTUNG DER MATERIALSTRUKTUR DES KNOCHENS. By PROF. DR. K.-H. KNESE, Anatomisches Institut der Universitaet Kiel. Pp. 56; 26 ills. Stuttgart: Georg Thieme Verlag, 1958 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $4.65.

THIS is an inquiry into the mechanical principles of the texture of bone. Decalcified cross-sections of femur, tibia, fibula, radius and ulna were studied by light microscopy, in polarized light, and with the phase contract technique. Punch cards were made of 47,690 osteons and evaluated by I.B.M. machine. It was found that the various orders of the bone texture, the fibers with their coat of apatite crystals, the lamellae, the osteons, and the higher systems, can all be interpreted technically as Verbundbau (reinforced construction) comparable to, but not identical with, that of steel reinforced concrete. The text is highly technical. It is well supplied with mathematical calculations. The illustrations are interesting. W.E.

NON-VENEREAL SYPHILIS. By ELLIS HERNDON HUDSON, M.D., D.T.M. & H. (LOND.), F.A.C.P., Emeritus Professor and Director of Health, Ohio University, Athens, Ohio. Pp. 204; 81 ills. Baltimore: The Williams & Wilkins Co., 1958. Price, $7.00.

FOR over four centuries the legend of the American origin of syphilis, transported by the crews of Columbus, has had its proponents. For fifty years a more significant controversy has centered about the question: are the treponemas of syphilis and yaws separate species, or are they the same, or at most minor variants of the same species? This book is a convincing presentation of the unitarian view. Based upon a lifetime study of the subject by the author, its central theme is that endemic non-venereal syphilis, which affects large proportions of certain backward rural populations of Southeastern Europe, Southwestern Asia and parts of Africa, furnishes a complete bridge between sporadic venereal syphilis of the modern world and yaws. He had many years of experience with bejel, the endemic syphilis of rural Arab populations in Deir-Ez-Zor, a community in the Syrian Desert on the bank of the Euphrates where cross the old caravan trails between Damascus and Mosul and between Aleppo and Bagdad. In an excellent chapter on "An Historical Perspective of Treponematosis," he develops the thesis that human treponematosis probably began in tropical Africa as a continuous manifestation (yaws), spread then to various regions of the world in the course of human migration, becoming modified in colder and more rugged climates to the endemic type of syphilis such as bejel, a non-venereal disease spread by contact and crowding and occurring largely among children. The emergence of syphilis as we know it was the result of the development of cities and the improvement in personal cleanliness. Subsequent chapters deal with the details of clinical, laboratory and experimental evidence upon which these conclusions are based. The author meticulously adduces each objection heretofore raised against the unitarian concept of treponematosis and answers them to the reviewer's satisfaction. The book

is written in a clear and entertaining style and the numerous illustrations, largely photographs of bejel lesions, are excellent. The book is recommended to all physicians and also to laymen interested in public health, biology and sociology. Doctor Hudson is to be congratulated upon this important contribution to medical knowledge and thinking. R.K.

THEORY OF PSYCHOANALYTIC TECHNIQUE. Clinic Monograph Series No. 12. By KARL MENNINGER, M.D., Director, Dept. of Education, The Menninger Foundation. Pp. 206; 15 ills. New York: Basic Books, Inc., 1958. Price, $4.75.

WRITTEN in his own clear inimitable style, Dr. Menninger presents a major contribution to the theory of psychoanalytic technique. The book is very readable and is clinically oriented.

The psychoanalytic treatment situation is referred to as the contract and the obligation of both parties in the transaction as discussed. Chapters III, IV and V of the book deals with regression, transference and countertransference and resistance. Chapter VI deals with interpretation and other intervention. Chapter VII refers to termination of the contract; that is, the separation of the two parties. A Bibliography and Index are included.

This book will appeal to persons with a serious interest in psychoanalysis. M.B.

CIBA FOUNDATION SYMPOSIUM ON THE CEREBROSPINAL FLUID. Editors for the Ciba Foundation, G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Chi., AND CECILIA M. O'CONNOR, B.Sc. Pp. 335; 141 ills. Boston: Little, Brown & Company, 1958. Price, $9.00.

THIS monograph on cerebrospinal fluid is published under the auspices of the Ciba Foundation. The production, circulation, and absorption of the cerebrospinal fluid is discussed by many eminent authorities. Nineteen of these were present at a symposium on this subject held in England in May, 1957.

The monograph is divided into 15 separate contributions on the subject and each contribution is followed by a discussion of the contribution by the entire group. Although space does not permit a listing of all the subjects, the following titles will give the reader a general idea of the subject matter:

The structural and functional changes in the telencephalic choroid plexus during human ontogenesis by J. Ariens Kappers.

The structure and relationships of the arachnoid granulations by Leslie Turner.

The fine structure of the mammalian choroid plexus by the late George Wislocki and A. J. Ladman.

Observations on the choroid plexus maintained as an organ in tissue culture by C. E. Lumsden.

Observations on the production and circulation of the cerebrospinal fluid by D. Woollam and J. W. Millen.

Studies of the formation and absorption of the cerebrospinal fluid using radioactive isotopes by B. Selverstone.

The reader will find in this monograph many important old and new contributions that have not been included in present day textbooks. The material is exceedingly stimulating and reflects the enormous amount of careful work that is being done on this fascinating subject. This monograph will prove rewarding to all interested in the cerebrospinal circulation and is heartily recommended. M.S.

LES SINUSITES DE L'ENFANCE. By J. TERRACOL, M.D., AND Y. GUERRIER, M.D., University of Montpellier. Pp. 166; 29 ills. Paris: Masson & Cie. 1958. Price, 1,400 Fr.

THIS systematic and comprehensive but concise monograph explores the frequency, significance and therapeutic problems of sinusitis in children and will be a valuable addition to the library of every rhinologist and pediatrician. After considering embryologic and anatomic factors, etiology is discussed in the light of infection, allergy, pharyngolymphoid structures, dental abnormalities, endocrine deficiencies and metabolic disorders. In enumerating the complications of sinusitis in children, spreading osteomyelitis is emphasized as a peculiar pathologic involvement in early life. Full coverage is given to methods of diagnosis and to current forms of local and systemic therapy including the use of steroid hormones. An English summary is appended. H.S.

INTERNATIONALES SYMPOSIUM ÜBER KLINISCHE CYTODIAGNOSTIK. Edited by PROF. DR. N. HENNING AND DR. S. WITTE, Med. Univ. Klinik, Erlangen. Pp. 216; 146 ills. 191 tables. Stuttgart: Georg Thieme Verlag, 1958 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $8.10.

THIS excellent book contains a comprehensive discussion by some 30 authors of various theoretical and practical aspects of clinical cytodiagnosis. The first part deals with electron-microscopy (Braunsteiner), histochemistry (Schümmelfeder), fluorescence microscopy and microspectroscopy (Trapp and others), and karymetry (Leibetseder). The second part is concerned with microscopic and photographic techniques including a description of the new automatic microphotographic microscope of Zeiss. The third and largest part of the book contains reviews of cytological studies of lymphnodes (Begemann), spleen (Lüdin), serous cavities (Riegel), liver (Bock), G.I. tract (Henning and others) and lungs (Grunze and others). Also, it contains a paper on oral epithelium and chromosomal sex (Kosenow). Exfoliative cytology of aspiration and puncture material is compared with histology of needle biopsies. The text is clear and well illustrated. This book is highly recommended to all physicians interested in clinical cytodiagnosis.

W.E.

ENTZÜNDUNG UND BLUTEIWEISSKÖRPER. By DR. H. ODENTHAL, Medizinische Akademie Düsseldorf. Pp. 115; 32 ills. Stuttgart: Georg Thieme Verlag, 1958 (Intercontinental Book Corporation, New York, U.S. Agents). Price, $4.65.

VARIOUS plasma proteins, including fibrinogen and C-reactive protein, were compared with the sedimentation rate, the circulating leukocytes, and the effect of various therapeutic measures in inflammation. Albumin and globulin were determined electrophoretically, fibrogen chemically. Acute inflammatory diseases were characterized by development during the first 24 hours of a primary inflammatory plasma protein reaction, that is, a rise in alpha-globulin, fibrinogen and C-reactive protein, and a fall in albumin, followed in 5 days or later by a secondary reaction, namely a rise in gamma-globulin. The latter was the outstanding reaction in chronic inflammatory diseases. The primary reaction was most severe in pneumonia and typhoid fever, and mildest in virus diseases. It was due most likely to damage of tissue. The secondary reaction was most marked in virus diseases. It appeared to be correlated with antibody formation. Granulocytosis and a shift to the left were associated generally with the primary reaction, lymphocytosis with the secondary reaction. An increase in sedimentation rate during the primary reaction was found to be conditioned by a rise in fibrinogen. Antibiotics and sulfonamides showed no direct effect upon the plasma proteins, while cytostatic and antirheumatic agents, such as ACTH, cortisone, Butazolidin and salicylic acid depressed the primary reaction by affecting the connective tissue, and the secondary reaction perhaps via antibody response. The book is recommended to clinicians interested in plasma proteins and inflammatory diseases.

W.E.

NEUROPATHOLOGY. By J. G. GREENFIELD, M.D., F.R.C.P., LL.D., Consulting Pathologist, National Hospital for Nervous Diseases, London; W. BLACKWOOD, M.B., Pathologist, National Hospital for Nervous Diseases, London; W. H. MCMENEMY, M.A., Pathologist, Maida Vale Hospital for Nervous Diseases, London; A. MEYER, M.D., Emeritus Professor of Neuropathology, University of London, and R. M. NORMAN, M.D., Neuropathologist, Burden Mental Research Dept., Frenchay Hospital, Bristol. Pp. 640; 364 ills. London: Edward Arnold Ltd., 1958 (The Williams & Wilkins Co., Baltimore, U.S. Agents). Price, $20.00.

THIS volume on Neuropathology by five contributors is divided into 13 chapters as follows:

(1) General pathology of the nerve cell and neuroglia (J. G. Greenfield).

(2) Vascular disease of the central nervous system (W. Blackwood).

(3) Infectious diseases of the central nervous system (J. G. Greenfield).

(4) Anoxias, intoxications and metabolic disorders (A. Meyer).

(5) Malformations of the nervous system, birth injury and diseases of early life (R. M. Norman).

(6) Traumatic lesions of the central and peripheral nervous systems (J. G. Greenfield).

(7) Demyelinating diseases (J. G. Greenfield).

(8) The dementias and progressive diseases of the basal ganglia (W. H. McMenemey).

(9) System degenerations of the cerebellum, brain stem, and spinal cord (J. G. Greenfield).

(10) Epilepsy (A. Meyer).

(11) Psychoses of obscure pathology (A. Meyer).

(12) Lesions of the nervous system associated with diseases or malformations of the cranium and spinal column (J. G. Greenfield).

(13) Diseases of the lower motor and sensory neurones (Peripheral neuritis and neuropathy) (J. G. Greenfield).

A list of books of reference is included at the end of the treatise.

This book is well illustrated and the authors have attempted to give more attention than usual to the history of the subject and some sections are largely based on the original descriptions of many of the clinical syndromes.

The price of the monograph appears unusually expensive considering that cerebral and spinal tumors have been left out completely because they are treated in a companion volume edited by Professor Dorothy S. Russell.

This textbook has much new material, is up-to-date and is an excellent addition to the books already published in this field. M.S.

Chemistry of Lipides as Related to Atherosclerosis. A Symposium. Compiled and edited by Irvine H. Page, M.D., Cleveland Clinic Foundation. Pp. 342; illustrated. Springfield, Ill.: Charles C Thomas, 1958. Price, $8.50.

This volume consists of a series of papers presented at an especially arranged symposium in May, 1957. The material is basically oriented, and the contributors are all recognized authorities in their respective fields. Included are discussions of triglycerides; phospholipides, sphingolipides; tissue and plasma lipoproteins; digestion and absorption; nutritional aspects; turnover of plasma lipides; fatty acids, their synthesis and their oxidation; the synthesis, transport, and metabolism of cholesterol; and clearing factor.

All who are interested in the broad area of lipides, particularly as they may be related to atherosclerosis, will find this a worthwhile summary of information available to the time of the symposium. C.Z.

Hermaphroditism, Genital Anomalies and Related Endocrine Disorders. By Howard W. Jones, Jr., M.D. and William Wallace Scott, M.D., Ph.D., Johns Hopkins University School of Medicine. Pp. 456; 466 ills. Baltimore: The Williams & Wilkins Company, 1958. Price, $16.00.

In recent years much has been learned about intersexuality and hermaphroditism. Rational modes of therapy have been developed so that today many forms of the disorder can be controlled or corrected.

The authors, a gynecologist, Dr. Jones, and a urologist, Dr. Scott, working in an institution where much of the pioneer work on this subject has been done, have had an opportunity to treat many of these patients. The text is well written and understandable and includes many case reports. There are numerous excellent photographs and drawings that aid the reader greatly in understanding the various clinical conditions.

This book should be of value to those interested in the problem of intersexuality or who may have occasion to encounter such a patient. B.C.

Geschlecht und Krankheit. By Prof. Dr. Max Bürger, Head, Medical Department, University of Leipzig. Pp. 516; 182 ills. and 151 tables. Munich: J. F. Lehmanns Verlag, 1958. Price, DM 60.

To do justice in a short review to this exhaustive treatise is impossible. The cooperation of many departmental specialists made it possible to cover a wide area. Part I presents studies insofar as known as to chemical differences, for the two sexes, of tissues (CNS, thyroid, muscles, nails, hair, tendons, blood, cholesterol, iron and copper metabolism); in particular the higher sulphur content of certain female tissues is pointed out. Part II stresses structural and functional differences for the two sexes, with special reference to circulation, respiration, renal action and sensory perceptions. Part III describes the differences encountered when function is disturbed and disease develops. And this is exemplified for the organ systems, infections, and reactions toward pharmacologic, alimentary, actinic, and thermic factors. The main thesis is that male and female, down to the last cell, are chemically, structurally and functionally different beings and that the reaction to disturbance of function is different. H.R.

Über die Erblichkeit des normalen Elektroencephalogramms. By Priv. Doz. Dr. med. F. Vogel, Max Planck Institut, Berlin. Pp. 92; 25 ills. Stuttgart: George Thieme Verlag. 1958 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $2.30.

This monograph is based upon a careful study of 208 pairs of twins (110 monozygotic and 98 dizygotic). Using a 16 channel electroencephalographic apparatus, records from 8 points could be made simultaneously from each of the twins. The electroencephalogram (EEG) was recorded in the resting state, during hyperventilation and anoxia,

and during sleep. For an analysis of the curves, the author developed some new methods, for example, measurement of the subalpha percentage, waves 133.3 msec. and longer, of the average amplitude and of the phase coordinates between both sites by means of a new planimeter. The studies show impressively the conformity of the EEGs of monozygotic and the great range of variation in the EEGs of dizygotic twins. In the last group there were only 17 of 96 pairs similar in general traits. The studies show the importance of heredity upon the EEG. E.S.

EXISTENCE: A NEW DIMENSION IN PSYCHIATRY AND PSYCHOLOGY. Edited by ROLLO MAY, ERNEST ANGEL AND HENRI F. ELLENBERGER. Pp. 445. New York: Basic Books, Inc., 1958. Price, $7.50.

EXISTENTIALISM, a philosophical system, developed after World War I, had a great upsurgence in Western European intellectual circles following the last great war. The existentialist approach attempts to examine man both in relation to himself and to his environment. Stress is placed on making man totally aware of the reality of his being and existence. An underlying tone of cynicism is apparent in all of the writings. Existential psychoanalysis is the name given to a method of psychotherapy based on the application of the principles of existentialism to the treatment of the neuroses and psychoses.

This book contains chapters on existential history, theory, methods of treatment and detailed case histories. each written by a prominent authority. Some of the writing suffers in translation, but on the whole, the book is quite readable. It must be considered as both a primer and handbook for those interested in the subject. H.D.

Year Book of Neurology, Psychiatry and Neurosurgery. Edited by ROLAND P. MACKAY, M.D., Professor of Neurology, University of Illinois (Neurology), S. BERNARD WORTIS, M.D., Professor of Psychiatry and Neurology, New York University-Bellevue Medical Center (Psychiatry), and OSCAR SUGAR, M.D., Associate Professor of Neurological Surgery (Neurosurgery). Pp. 624; 104 ills. Chicago: The Year Book Publishers, Inc., 1958. Price, $8.00.

THIS edition maintains the standard set by the previous issues. It presents in clear concise form and frequently well illustrated the articles published in the literature in 1957, which the authors believe will be of most interest to those in the fields of Neurology, Psychiatry, and Neurosurgery.

The reviews are long enough to give the reader an excellent idea of the complete contents of the original article and yet short enough to save the reader considerable time in reviewing the highlights in his field.

This book is recommended to all interested in the field of Neurology, Psychiatry, or Neurosurgery. M. S.

Antibiotics Annual, 1957–1958. Edited by HENRY WELCH, PH.D., AND FELIX MARTI-IBANEZ, M.D. Pp. 1070; illustrated. New York: Medical Encyclopedia, Inc., 1958. Price, $12.00.

THIS volume is comprised of papers presented at the Fifth Annual Symposium on Antibiotics. The conference was held under the auspices of the Food and Drug Administration in Washington, D.C., in late September and early October, 1957. Many antibiotics, new and old, are discussed from both clinical and laboratory aspects. In addition to the papers dealing with specific antibiotics, there are included valuable panel discussions on rheumatic fever prophylaxis, host resistance and chemotherapy, and antibiotics as antitumor and antiviral substances.

All who are concerned with infectious disease problems will find a treasure of information in this carefully edited volume. C. Z.

Biology of the Treponematoses. WHO Monograph Series No. 35. BY THOMAS BOURNE TURNER, Professor of Microbiology, and DAVID H. HOLLANDER, Assistant Professor of Microbiology, Johns Hopkins University. Pp. 278; 13 ills. and 2 color plates. Geneva: World Health Organization. 1957. Price, $6.00.

THIS is an up-to-date monograph on treponemal diseases which still are to be listed among the major afflictions of mankind. The treponemes are considered on the basis of the experimental disease produced by them in laboratory animals, their characteristics *in vitro;* and their immunity phenomena. In addition, the response of these organisms to drugs is discussed comprehensively.

Microbiologists and others concerned with this group of organisms will find this an authoritative and informative treatise. C. Z.

Biochemistry of Some Peptide and Steroid Antibiotics. BY E. P. ABRAHAM. Pp. 96; 10 ills. New York: John Wiley & Sons, Inc., 1957. Price, $3.00.

THE lectures in microbial biochemistry which were presented in the spring of 1957 at the Institute of Microbiology, Rutgers University, have been published in this small volume. Included are comprehensive discussions of the bacitracins, the cephalosporins, and of the structural and functional relationships of these substances to other antibiotics.

This is a valuable treatise for workers who are concerned with the more basic biochemical aspects of antibiotics. C. Z.

Methods in Medical Research, Volume 7. Edited by J. V. WARREN. Pp. 237; illustrated. Chicago: Year Book Publishers, Inc., 1958. Price, $7.50.

THE latest in this valuable series of reference guides to methods in medical research offers descriptions of techniques for use in four areas of investigation. These are 1) Chemical Investigation of Muscular Tissue; 2) Hemodynamic Methods—Heart and Lungs; 3) Methods for the Study of Human Leukocytes; and, 4) Methods for Study of the Histology and Cytology of the Retina.

This volume should be helpful to those concerned with research in one or more of these fields. C. Z.

Advances in Virus Research, Vol. V. Edited By KENNETH M. SMITH AND MAX A. LAUFFER. Pp. 376; illustrated. New York: Academic Press, Inc., 1958. Price, $9.50.

THIS is the fifth in a series of volumes which review research progress in studies of viruses of plants and animals. Among the topics considered in the present volume are the Psittacosis-Lymphogranuloma Group of Viruses, the Measurement of Complement Fixation by Viruses, and the Mechanism of Hemagglutination by Influenza Virus.

Workers in microbiology will find much of interest in these basically oriented reviews. C. Z.

Menschliche und Tierische Gewebsthrombokinasen. By DR. H. A. THIES. Pp. 56; 12 ills. Stuttgart: Georg Thieme Verlag, 1957 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $2.25.

THE properties and importance of thrombokinase in the clotting mechanism are reviewed in this monograph. Those students of blood coagulation, who read German, will find much of interest in this small book. C. Z.

Le Volume Sanguin des Poumons Chez L-Homme. By JACQUES LAMMERANT, Université de Louvain. Pp. 171; 33 ills. Brussels: A Christiaens, Editions Arscia, 1957.

THIS is an excellent French publication on pulmonary blood volume in man. The question of pulmonary blood volume is well stated and the fundamental methods used to delineate this parameter are clearly described. Since pulmonary blood volume (Stewart) can be determined from the cardiac output and pulmonary circulation time the advantages of the dye-dilution method are stressed. This method permits a simultaneous measure of pulmonary circulation time and cardiac output. The use of radioisotopes is described as an application of the Stewart Method. For this purpose the figures are valuable. Studies in exercise and heart disease are included. M. O.

The Atomic Age and Our Biological Future. By H. V. BRONDSTED. Translated by E. M. HUGGARD. Pp. 80. New York: Philosophical Library, Inc., 1958. Price, $2.75.

THE social and biological hazards that are inherent in the peaceful as well as military uses of atomic energy are discussed in this small volume. It is written in popular style in an effort to reach large segments of the population. The author deliberately paints a gloomy picture: "When one is dealing with dangerous things, it is better to be over-cautious than too daring. Radiation is dangerous."

This book presents the author's views very clearly. It should be read, however, with the realization that the positive, beneficial aspects of atomic energy are not considered. C. Z.

Topics in Microbial Chemistry: Antimycin, Coenzyme A, Kinetin and Kinins. By F. M. STRONG, University of Wisconsin. Pp. 166; 35 ills. New York: John Wiley & Sons, Inc.; London: Chapman & Hall, Ltd., 1958. Price, $5.00.

THIS booklet contains three lectures delivered in 1956 as the first in a series to be known as the E. R. Squibb Lectures on Chemistry of Microbial Products. The three unrelated substances discussed in them are: Antimycin, an antifungal antibiotic derived from species of actinomyces; Coenzyme A, a bound form of pantothenic acid; Kinetin and Kinins, a plant growth hormone and its analogues. These well documented discussions by an outstanding investigator will be welcomed by microbial physiologists and biochemists. E. S.

A Manual of Pharmacology. By TORALD SOLLMANN, M.D., Professor Emeritus of Pharmacology and Materia Medica, Western Reserve University. 8th ed. Pp. 1535. Philadelphia: W. B. Saunders Co., 1957. Price, $20.00.

IT is a pleasure to greet the 8th edition of this text which has been a standard in its field since the appearance of the first edition in 1917. Well nigh encyclopedic in scope, with far more subject matter than most texts in that field have, the book has great value as a reference work. At the same time the author, with nice discrimination, has put in ordinary type the material that all students should aim to know, while the more detailed data, to be consulted only as occasion arises, and comprising the great bulk of the volume, are in somewhat smaller type. The book is highly recommended to all physicians and students. R.K.

Diagnostic Laboratory Hematology. By GEORGE E. CARTWRIGHT, M.D., Professor of Medicine, University of Utah College of Medicine. 2nd ed. Pp. 250; 33 ills. New York: Grune & Stratton, Inc., 1958. Price, $6.75.

THIS is a timely revision and extension of an excellent text of laboratory methods of value in the diagnosis of hematologic disorders. Included in the present edition are photometric methods for the determination of hemoglobin, heme pigments in serum, osmotic fragility, and serum bilirubin; a method for counting platelets with the phase contrast microscope; and techniques for paper electrophoresis of hemoglobins.

Each method is described in a clear, concise manner. The interpretive explanations which are offered for the respective test results are generally excellent, though that for heterophile agglutination leaves something to be desired.

Medical students, technologists, and practicing physicians will find this a reliable guide for many useful hematologic procedures. C.Z.

Bailey's Textbook of Histology. Revised and edited by WILFRED M. COPENHAVER, PH.D., Columbia University College of Physicians and Surgeons, and DOROTHY D. JOHNSON, PH.D., Columbia University College of Physicians and Surgeons. 14th ed. Pp. 599; 478 ills. Baltimore: The Williams & Wilkins Co., 1958. Price, $11.00.

THIS revised fourteenth edition of Bailey's Textbook of Histology is geared to the needs of first year students in histology. It is elementary in scope and hence, no source of information for teachers or researchers. Its approach is morphological rather than functional with no emphasis on the physiology or biochemistry of tissues. The illustrations are fair but not outstanding. The number of editions which this book enjoyed, however, indicates that it is well received by teachers and students in histology. W.E.

Eye Surgery. BY H. B. STALLARD, M.B.E., M.A., M.D. (CANTAB.), F.R.C.S. (ENG.), HON. LL.D. (ST. ANDREWS). 3rd ed. Pp. 899; 671 ills. Baltimore: The Williams & Wilkins Co., 1958. Price, $18.00.

THIS book is an old standby and a welcome addition to any library. This, the third, edition has been brought up-to-date and several new features have been added.

The sections revised or added are those dealing with anesthesia; corneal transplant; Ridley's operation; and treatment of intraocular neoplasms. Much of this book is a digest of the operations and techniques found most satisfactory by the author. This makes it valuable because those procedures found lacking are soon dropped.

A book of this type gives an American ophthalmologist a continental viewpoint, broadening his horizon and enabling him to keep abreast of what is going on a few thousand miles away.

You will like this book. L.H.

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